STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 171887

TO:	From:
Rei-Tsang Shiao Location: 5a10 / 5c18 Wednesday, December 07, 2005 Art Unit: 1626 Phone: 571-272-0707 Serial Number: 10 / 627519	Jan Delaval Location: Biotech-Chem Library Remsen 1a51 Phone: 571-272-2504 jan.delaval@uspto.gov

Search Notes

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NOV 17 2005

TC1700/CHEM. DIVISION (STIC)

Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: Robert (Reuben) Shiao Examiner #: 79521 Date: 11/17/05

Art Unit: 1626 Phone Number: 2-0709 Serial Number: 10/629,519

Location (Bldg/Room#): REM (Mailbox #): 54/6C18 Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: compositions containing a ruthenium complex

Inventors (please provide full names): Keppler et al

Earliest Priority Date:

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

I search compositions comprising cpd I, and cpd II, (see claim 33, & also see example 1)

$M\ [Ru X B(H_2O)_p(OH)_q(O)_r]_{2r+1}$ cpd I

* M is metal
X is halogen HCO3, R CO (R is alkyl, alkylene)
* B is heterocyc ie, imidazole, pyridine, triazol, indaz
* p, q r = 0, 0.5

$B(HX)_s$ cpd II

* B is same as cpd I
X is same as cpd I
s is integer

I process of making coposition and method of use of the compositions.

****

STAFF USE ONLY

Searcher: Jan

Searcher Phone #: 22504

Searcher Location:

Date Searcher Picked Up: 12/7/05

Date Completed: 12/7/05

Searcher Prep & Review Time: 70

Online Time: 455

Type of Search

___ NA Sequence (#)
___ AA Sequence (#)
✓ Structure (#)
___ Bibliographic
___ Litigation
___ Fulltext
___ Other

Vendors and cost where applicable

✓ STN ___ Dialog
___ Questel/Orbit ___ Lexis/Nexis
___ Westlaw ___ WWW/Internet

___ In-house sequence systems

___ Commercial ___ Oligomer ___ Score/Length
___ Interference ___ SPDI ___ Encode/Transl
___ Other (specify)

STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact ***the searcher or contact***:

Mary Hale, Information Branch Supervisor
Remsen Bldg. 01 D86
571-272-2507

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* ☐ *Example: 1610*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
  (journal articles, conference proceedings, new product announcements etc.)

- *Relevant prior art **not found**:*
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC-Biotech-Chem Library Remsen Bldg.

L3 ANSWER 17 OF 34 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:550474 CAPLUS
DOCUMENT NUMBER: 131:280631
TITLE: Synthesis of tumor-inhibiting complex salts containing the anion trans-tetrachlorobis(indazole)ruthenate(III) and crystal structure of the tetraphenylphosphonium salt
AUTHOR(S): Peti, Wolfgang; Pieper, Thomas; Sommer, Martina; Keppler, Bernhard K.; Giester, Gerald
CORPORATE SOURCE: Institute General Inorganic Chemistry, Univ. Vienna, Vienna, A-1090, Austria
SOURCE: European Journal of Inorganic Chemistry (1999), (9), 1551-1555
CODEN: EJICFO; ISSN: 1434-1948
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Indazolium trans-tetrachlorobis(indazole)ruthenate(1-) exhibits excellent results against different tumor models in vitro and in vivo. To improve the water solubility necessary for the introduction of this tumor-inhibiting compound into clin. trials, the authors synthesized the corresponding Na salt in a 2-step ion exchange via the tetramethylammonium salt. The Na salt shows a 3,5-fold higher solubility in water relative to the indazolium salt. The authors also synthesized the n-butylammonium, n-octylammonium, and tetraphenylphosphonium salts, all of which showed improved solubility in organic solvents. The x-ray crystal structure of the latter could be solved, proving the trans configuration of the complex anion (triclinic, P.hivin.1, a = 11.000(2), b = 13.503(2), c = 14.471(2) Å, α = 65.42(1), β = 82.80(1), γ = 67.93(1)°, V = 1810.2 Å3, Z = 2, ρc = 1.50 g/cm3, μ(MoKα) = 8.1, 5573 observed reflections with Fo > 4σ(Fo), 562 refined parameters, R1 = 0.033, wR2 = 0.088). In spite of the paramagnetic Ru(III) center an assignment of the coordinated indazole protons could be made with the help of a COSY experiment

IT **124875-20-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant for preparation of tetraphenylphosphonium trans-tetrachlorobis(indazole)ruthenate(III))

RN 124875-20-3 CAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

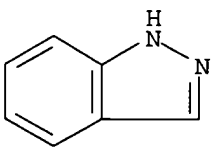
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



```
=> fil reg
FILE 'REGISTRY' ENTERED AT 15:40:44 ON 07 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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provided by InfoChem.

STRUCTURE FILE UPDATES:    6 DEC 2005  HIGHEST RN 869462-96-4
DICTIONARY FILE UPDATES:   6 DEC 2005  HIGHEST RN 869462-96-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> d ide can 135

L35  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   124875-20-3  REGISTRY
ED   Entered STN:  19 Jan 1990
CN   Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-,
     hydrogen, compd. with 1H-indazole (1:1) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-Indazole, mono[(OC-6-11)-tetrachlorobis(1H-indazole-
     κN2)ruthenate(1-)] (9CI)
CN   1H-Indazole, mono[(OC-6-11)-tetrachlorobis(1H-indazole-N2)ruthenate(1-)]
     (9CI)
CN   Ruthenate(1-), tetrachlorobis(1H-indazole-N2)-, (OC-6-11)-, hydrogen,
     compd. with 1H-indazole (1:1)
OTHER NAMES:
CN   KP 1019
DR   123391-22-0
MF   C14 H12 Cl4 N4 Ru . C7 H6 N2 . H
SR   CA
LC   STN Files:   ADISNEWS, BIOSIS, CA, CAPLUS, CASREACT, IMSRESEARCH, PHAR,
       TOXCENTER, USPATFULL
```

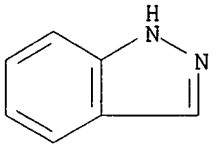
CM 1

CRN 124875-19-0 (189556-38-5)
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

34 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
34 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 143:259727

REFERENCE 2: 143:241328

REFERENCE 3: 143:52892

REFERENCE 4: 142:441275

REFERENCE 5: 142:385348

REFERENCE 6: 142:385260

REFERENCE 7: 142:254042

REFERENCE 8: 141:385463

REFERENCE 9: 141:81839

REFERENCE 10: 140:296757

=> => d sta que l31
L4 4 SEA FILE=REGISTRY ABB=ON PLU=ON (124875-20-3/BI OR 197723-00-5/BI OR 63725-55-3/BI OR 7440-18-8/BI)
L5 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND CCS/CI
L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 189556-38-5
L7 9 SEA FILE=REGISTRY ABB=ON PLU=ON 189556-38-5/CRN
L23 61 SEA FILE=REGISTRY ABB=ON PLU=ON (16.515.9/RID OR 16.213.11/RID OR 16.213.5/RID OR 16.515.1/RID OR 16.213.3/RID OR 16.213.4/RID OR 16.213.8/RID OR 16.515.11/RID OR 16.515.2/RID OR 16.515.22/RID OR 16.515.7/RID) AND RU/ELS
L25 816 SEA FILE=REGISTRY ABB=ON PLU=ON (333.161.31 OR 16.165.12 OR

```
                16.195.24)/RID AND RU/ELS
L26           877 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L23 OR L25)
L27               STR

Ru^Hy
1   2


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M1 N  AT   2

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   2

STEREO ATTRIBUTES: NONE
L29           245 SEA FILE=REGISTRY SUB=L26 SSS FUL L27
L30             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND RU/ELS NOT RU/MF
L31           245 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L5 OR L6 OR L7 OR L30 OR
                  L29)


=> d his

     (FILE 'HOME' ENTERED AT 14:51:11 ON 07 DEC 2005)
                SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 14:51:18 ON 07 DEC 2005
L1              1 S US20050032801/PN OR (US2003-627519 OR WO2002-EP863 OR DE2001-
                E KEPPLER B/AU
L2            219 S E3-E10
                E KEPLER B/AU
                E FAUSTUS/PA,CS
L3             14 S E3-E16
                SEL RN L1

     FILE 'REGISTRY' ENTERED AT 14:52:52 ON 07 DEC 2005
L4              4 S E1-E4
L5              1 S L4 AND CCS/CI
L6              1 S 189556-38-5
L7              9 S 189556-38-5/CRN
L8              1 S L4 NOT RU/ELS
L9              1 S PYRAZOLE/CN
                E INDAZOLE/CN
L10             1 S E3
                E IMIDAZOLE/CN
L11             1 S E3
                E TRAZOLE/CN
                E TRIAZOLE/CN
L12             1 S E3
L13          1407 S (N3C2 OR N2CNC)/ES AND 1/NR AND 3/ELC.SUB
L14            71 S L13 AND 3/N AND 2/C
L15            51 S L14 AND 1/NC
L16            44 S L15 AND (C AND N AND H)/ELS
L17            41 S L16 NOT (PMS OR IDS)/CI
L18            31 S L17 NOT ((D OR T)/ELS OR 11C# OR 13C# OR 14C# OR C11# OR C13#
L19            26 S L18 NOT RPS/CI
L20            22 S L19 NOT ION
L21            21 S L20 NOT 15N2
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L22          16 S L21 NOT IUM
                SEL RID
L23          61 S E1-E11 AND RU/ELS
L24        3025 S (333.161 OR 16.165 OR 16.195)/RID AND RU/ELS
L25         816 S (333.161.31 OR 16.165.12 OR 16.195.24)/RID AND RU/ELS
L26         877 S L23,L25
L27             STR
L28          12 S L27 SAM SUB=L26
L29         245 S L27 FUL SUB=L26
                SAV TEMP L29 SHIAO627/A
L30           2 S L4 AND RU/ELS NOT RU/MF
L31         245 S L5-L7,L30,L29

     FILE 'HCAPLUS' ENTERED AT 15:08:16 ON 07 DEC 2005
L32         191 S L31
L33          54 S L32 AND L1-L3
L34          13 S KP1019 OR KP 1019

     FILE 'REGISTRY' ENTERED AT 15:09:26 ON 07 DEC 2005
L35           1 S 124875-20-3

     FILE 'HCAPLUS' ENTERED AT 15:09:35 ON 07 DEC 2005
L36          34 S L35
L37          36 S L34,L36
L38          25 S L37 AND (PY<=2001 OR PRY<=2001 OR AY<=2001)
L39         133 S L32 AND (PY<=2001 OR PRY<=2001 OR AY<=2001)
L40         131 S L32 AND (PD<=20010126 OR PRD<=20010126 OR AD<=20010126)
L41          25 S L37 AND (PD<=20010126 OR PRD<=20010126 OR AD<=20010126)
L42          68 S L31(L)PREP+NT/RL
L43          86 S L31(L)(THU OR BAC OR DMA OR PAC OR PKT)/RL
L44         117 S L32 AND (PHARMACEUT? OR PHARMACOL? OR PATHOL?)/SC,SX,CW,CT
                E NEOPLASM INHIBITOR/CT
L45       77032 S E4-E6
                E E4+ALL
                E E2+ALL
L46      182155 S E3 OR E41+OLD,NT OR E42+OLD,NT OR E43+OLD,NT OR E45+OLD,NT
L47          65 S L39 AND L45,L46
L48          28 S L37 AND L45,L46
L49          18 S L41 AND L48
L50          74 S L42-L44 AND L47-L49
L51          33 S L1-L3 AND L37
L52          40 S L33,L51 AND L40,L41
L53          84 S L50,L52
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:17:34 ON 07 DEC 2005
L54          59 S E1-E59
L55          11 S L54 AND S/ELS
L56          48 S L54 NOT L55
L57           6 S L56 AND (C28H24CL2N8RU OR C3H4CL4N3ORU)
L58          42 S L56 NOT L57
L59           3 S L58 AND (C21H18CL3N6RU OR C16H15CL3N5RU)
L60          39 S L58 NOT L59

     FILE 'HCAPLUS' ENTERED AT 15:31:46 ON 07 DEC 2005
L61          78 S L60
L62          61 S L61 AND (PD<=20010126 OR PRD<=20010126 OR AD<=20010126)
L63          45 S L62 AND L45,L46
L64          32 S L60 (L) (THU OR BAC OR DMA OR PAC OR PKT)/RL AND L62
L65          53 S L62 AND (PHARMACEUT? OR PHARMACOL? OR PATHOL?)/SC,SX,CW,CT
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L66          40 S L1-L3 AND L62
L67          61 S L41,L62-L66
L68          54 S L67 NOT P/DT
L69           7 S L67 NOT L68
L70           5 S L69 NOT (IMMUNOSUPP? OR HYPERPROLIFERAT?)
L71          36 S L68 AND L1-L3
L72           2 S L71 NOT ?TUMOR?
L73          34 S L71 NOT L72
L74          18 S L68 NOT L69-L73
L75           3 S L74 NOT ?TUMOR?
L76          15 S L74 NOT L75
L77          54 S L70,L73,L76

     FILE 'MEDLINE' ENTERED AT 15:36:54 ON 07 DEC 2005
L78           8 S L34 OR L35
L79           2 S L78 AND PY<=2001
L80           2 S L79 AND KEPPLER ?/AU

     FILE 'CANCERLIT' ENTERED AT 15:38:08 ON 07 DEC 2005
L81           3 S L78
L82           1 S L81 NOT MEDLINE/OS
L83           1 S L82 AND KEPPLER ?/AU

     FILE 'EMBASE' ENTERED AT 15:38:39 ON 07 DEC 2005
L84          12 S L78
L85          16 S "INDAZOLIUM TETRACHLOROBIS(INDAZOLE)RUTHENATE"/CT
L86          11 S L84,L85 AND PY<=2001
L87           4 S L86 AND KEPPLER ?/AU
L88          11 S L86,L87
L89          11 S L88 AND (?NEOPLAS? OR ?TUMOR? OR ?CANCER?)

     FILE 'REGISTRY' ENTERED AT 15:40:44 ON 07 DEC 2005

=> dup rem l80 l83 l89
FILE 'MEDLINE' ENTERED AT 15:41:27 ON 07 DEC 2005

FILE 'CANCERLIT' ENTERED AT 15:41:27 ON 07 DEC 2005

FILE 'EMBASE' ENTERED AT 15:41:27 ON 07 DEC 2005
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PROCESSING COMPLETED FOR L80
PROCESSING COMPLETED FOR L83
PROCESSING COMPLETED FOR L89
L90          12 DUP REM L80 L83 L89 (2 DUPLICATES REMOVED)
                ANSWERS '1-2' FROM FILE MEDLINE
                ANSWER '3' FROM FILE CANCERLIT
                ANSWERS '4-12' FROM FILE EMBASE

=> d all tot

L90  ANSWER 1 OF 12     MEDLINE on STN                  DUPLICATE 1
AN   1998230618     MEDLINE
DN   PubMed ID: 9570691
TI   Comparative nephrotoxicity of some antitumour-active platinum and
     ruthenium complexes in rats.
AU   Kersten L; Braunlich H; Keppler B K; Gliesing C; Wendelin M;
     Westphal J
CS   Institute of Pharmacology and Toxicology, Friedrich Schiller University,
     Jena, Germany.. hzub@mti-n.uni-jena.de
SO   Journal of applied toxicology : JAT, (1998 Mar-Apr) 18 (2)
```

93-101.
Journal code: 8109495. ISSN: 0260-437X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980604
AB The nephrotoxicity of three platinum (CPL, KP734, KP735) and three ruthenium coordination complexes (KP418, KP692, **KP1019**) was tested in rats in comparison to cisplatin (CP). Renal functional changes (excretion of water, protein, p-aminohippurate (PAH) and osmolytes) were not observed after the administration of 10% of the LD450 of the compounds given twice a week for up to 5 weeks. After a relatively high single dose of the substances (50% of the LD50), signs of nephrotoxicity on the day of maximal renal damage decreased in the following order: CP, KP418, CPL, KP734, KP735, KP692 and **KP1019**. In comparison to CP, proteinuria was significantly lower after the administration of any of the compounds, especially KP692 and **KP1019**. Neither renal lipid peroxidation (TBARS) nor glutathion status (GSH, GSSG) was affected. In summary, KP735 in the group of platinum complexes and **KP1019** in the ruthenium group had the lowest nephrotoxicity. Other investigators have shown that all complexes induced anti-neoplastic activity under analogous experimental conditions.
CT Check Tags: Comparative Study; Female
Animals
*Antineoplastic Agents: TO, toxicity
Cisplatin: TO, toxicity
*Kidney: DE, drug effects
Lipid Peroxidation: DE, drug effects
*Platinum Compounds: TO, toxicity
Proteinuria: CI, chemically induced
Rats
Rats, Wistar
*Ruthenium Compounds: TO, toxicity
RN 15663-27-1 (Cisplatin)
CN 0 (Antineoplastic Agents); 0 (Platinum Compounds); 0 (Ruthenium Compounds)

L90 ANSWER 2 OF 12 MEDLINE on STN DUPLICATE 2
AN 1998279246 MEDLINE
DN PubMed ID: 9616290
TI Preclinical activity of trans-indazolium[tetrachlorobisindazoleruthenate(III)] (NSC 666158; IndCR; **KP 1019**) against tumour colony-forming units and haematopoietic progenitor cells.
AU Depenbrock H; Schmelcher S; Peter R; **Keppler B K**; Weirich G; Block T; Rastetter J; Hanauske A R
CS Technische Universitat Munchen, Klinikum rechts der Isar, Abteilung Hamatologie und Onkologie, Germany.
SO European journal of cancer (Oxford, England : 1990), **(1997 Dec)** 33 (14) 2404-10.
Journal code: 9005373. ISSN: 0959-8049.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980625
Last Updated on STN: 19980625

Entered Medline: 19980616

AB Trans-indazolium[tetrachlorobisindazoleruthenate(III)] (**KP 1019**) is a new heavy metal complex with promising activity against tumour cell lines and in animal models. We studied the antineoplastic effects of **KP 1019** (final concentrations: 1, 10, 100 micrograms/ml) on in vitro proliferation of clonogenic cells from freshly explanted human tumours in a capillary soft agar cloning system, and compared the activity of **KP 1019** with conventional antineoplastic agents. 53 of 75 specimens (71%) showed adequate growth in controls. **KP 1019** inhibited tumour colony formation in a concentration-dependent manner in both short- (1 h) and long-term (21 d) exposure experiments. **KP 1019** at 100 micrograms/ml with 1 h exposure was as active as bleomycin, cisplatin, doxorubicin, etoposide, 5-fluorouracil, methotrexate, mitomycin-C and vinblastine, with only paclitaxel more active than **KP 1019** (P = 0.002). The antitumour activity of **KP 1019** was more pronounced after long-term exposure, indicating the potential schedule dependency of **KP 1019**. Activity was observed against non-small cell lung, breast and renal cancer. We conclude that if appropriate plasma levels can be achieved in patients, **KP 1019** may have significant clinical activity against a variety of different tumour types.

CT Cell Division: DE, drug effects
Dose-Response Relationship, Drug
Hematopoietic Stem Cells: CY, cytology
*Hematopoietic Stem Cells: DE, drug effects
Humans
*Indazoles: PD, pharmacology
*Organometallic Compounds: PD, pharmacology
Tumor Cells, Cultured
Tumor Stem Cell Assay
*Tumor Stem Cells: DE, drug effects
Tumor Stem Cells: PA, pathology

CN 0 (Indazoles); 0 (Organometallic Compounds); 0 (indazolium-tetrachlorobisindazoleruthenate(III))

L90 ANSWER 3 OF 12 CANCERLIT on STN
AN 96603387 CANCERLIT
DN 96603387
TI Effects of trans-indazolium [tetrachlorobis-indazole ruthenate (III); **KP 1019**] on clonogenic growth of freshly explanted human tumors (Meeting abstract).
AU Depenbrock H; Schmelcher S; Peter R; **Keppler B K**; Fellbaum C; Block T; Rastetter J; Hanauske A R
CS Technische Universitat Munchen, D-81664 Munchen, Germany.
SO Proc Annu Meet Am Soc Clin Oncol, (1995) 14 A1621.
ISSN: 0732-183X.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199604
ED Entered STN: 19970509
Last Updated on STN: 19970509

AB We have studied the antineoplastic effects of **KP 1019** (final concentrations: 1, 10, 100 ug/ml) on in vitro proliferation of clonogenic cells from freshly explanted human tumors in a capillary soft agar cloning system. Using short-term (1 hr) and long-term (21 days) exposures, we have compared the activity of **KP 1019** with conventional antineoplastic agents. 51 of 75 specimens (68%) showed adequate growth in controls (10 breast, 8 kidney, 5 lung, 4 testis, 24 other tumor types). Using the short-term exposure schedule, **KP**

1019 inhibited tumor colony formation in a concentration-dependent manner with 1/51 specimens (2%) inhibited at 1 ug/ml, 3/51 (6%) at 10 ug/ml and 21/51 specimens (41%) inhibited at 100 ug/ml. At 100 ug/ml, **KP 1019** was as active as bleomycin, cisplatin, doxorubicin, etoposide, 5-fluorouracil, interferon-alpha 2, methotrexate, mitomycin-C, and vinblastine. Paclitaxel was significantly more active than **KP 1019** (p=0.002). Using the long-term exposure schedule, **KP 1019** inhibited tumor colony formation in a concentration dependent manner with 6/51 specimens (12%) inhibited at 1 ug/ml, 14/51 (28%) at 10 ug/ml and 41/51 specimens (80%) inhibited at 100 ug/ml. We conclude that **KP 1019** has activity against freshly explanted clonogenic tumor cells. Higher activity in long-term exposure indicates schedule-dependency of **KP 1019**. Further clinical development of this agent seems warranted.

RN 33069-62-4 (Paclitaxel); 7440-18-8 (Ruthenium)
CN 0 (Antineoplastic Agents)

L90 ANSWER 4 OF 12 EMBASE
AN 2000180366 EMBASE
TI [New substances in oncology. Report of the joint annual meeting of the German and Austrian Societies for Hematology and Oncology in Jena]. NEUE SUBSTANZEN IN DER ONKOLOGIE. BERICHT VON DER GEMEINSAMEN JAHRESTAGUNG DER DOGHO, JENA.
AU Barth J.
CS J. Barth, Apotheker fur Klinische Pharmazie, Apoth. Univ. Klin. Gesamthochschule, Hufelandstr. 55, 45122 Essen, Germany
SO Krankenhauspharmazie, (2000) Vol. 21, No. 5, pp. 218-229.
Refs: 21
ISSN: 0173-7597 CODEN: KRANDZ
CY Germany
DT Journal; Conference Article
FS 016 Cancer
037 Drug Literature Index
LA German
ED Entered STN: 20000615
Last Updated on STN: 20000615
CT Medical Descriptors:
***cancer: DT, drug therapy**
cancer chemotherapy
antineoplastic activity
melanoma: DT, drug therapy
lung carcinoma: DT, drug therapy
glioblastoma: DT, drug therapy
human
conference paper
Drug Descriptors:
*new drug
***antineoplastic agent: DT, drug therapy**
fluoropyrimidine derivative: DT, drug therapy
fluoropyrimidine derivative: PO, oral drug administration
tegafur: DT, drug therapy
tegafur: PO, oral drug administration
capecitabine: DT, drug therapy
capecitabine: PO, oral drug administration
ruthenium complex: DT, drug therapy
indazolium tetrachlorobis(indazole)ruthenate: DT, drug therapy
platinum derivative: DT, drug therapy
kp 735: DT, drug therapy

gallium
kp 46: DT, drug therapy
gallium derivative: DT, drug therapy
dolastatin: DT, drug therapy
dolastatin derivative: DT, drug therapy
cematodin: DT, drug therapy
purine nucleoside: DT, drug therapy
pentostatin: DT, drug therapy
antisense oligonucleotide: DT, drug therapy
irinotecan: DT, drug therapy
topotecan: DT, drug therapy
antimetabolite: DT, drug therapy
tomudex: DT, drug therapy
rituximab: DT, drug therapy
edrecolomab: DT, drug therapy
tumor vaccine: DT, drug therapy
unclassified drug

RN (tegafur) 17902-23-7; (capecitabine) 154361-50-9; (gallium) 7440-55-3; (pentostatin) 53910-25-1; (irinotecan) 100286-90-6; (topotecan) 119413-54-6, 123948-87-8; (tomudex) 112887-68-0; (rituximab) 174722-31-7
CN Ftorafur; Xeloda; Kp 735; Kp 46; **Kp 1019**; Tomudex; Panorex; Mabthera; Hycamtin

L90 ANSWER 5 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 97022396 EMBASE
DN 1997022396
TI Synthesis, characterization and solution chemistry of trans-indazoliumtetrachlorobis(indazole)ruthenate(III), a new **anticancer** ruthenium complex. IR, UV, NMR, HPLC investigations and **antitumor** activity..
AU Lipponer K.-G.; Vogel E.; **Keppler B.K.**
CS K.-G. Lipponer, Institute of Inorganic Chemistry, University of Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany
SO Metal-Based Drugs, (1996) Vol. 3, No. 5, pp. 243-260.
Refs: 22
ISSN: 0793-0291 CODEN: MBADEI
CY Israel
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 970214
Last Updated on STN: 970214
AB Besides intensive studies into the synthesis of the complex trans-HInd[RuCl4(ind)2] (Ind = indazole) 1, which differs remarkably from the usual method for the complexes of the HL[RuCl4L2]-type, competitive products and hydrolysis of this species are described. Stability and pseudo-first-order rate constant under physiological conditions of complex 4 in comparison with the analogous imidazole complex trans-Hlm[RuCl4(im)2] (Im = imidazole) ICR were examined by means of HPLC, UV and conductivity measurements (k(cbs) (1) = 1.55 x 10-4 s-1; k(cbs) (ICR) = 9.10 x 10-4 s-1). An attempt was made to elucidate the bonding conditions in 1 by studying the reactions of Ru(III) and the two N-methyl isomers of indazole. It can be expected that bonding in the unsubstituted ligand should occur via the N2 nitrogen. The molecular structures of the complex trans-H(1-MeInd)[RuCl4(1-MeInd)2] x 1H2O (1-MeInd = 1-methylindazole) 6 and its hydrolysis product in aqueous solution [RuCl3(H2O)(1-MeInd)2] 7

were determined crystallographically. After anisotropic refinement of F values by least squares, R is 0.053 for 6 and 0.059 for 7. Both complexes crystallize with four molecules in a unit cell, of monoclinic symmetry. The space group is P2.1/n for 6 with cell dimensions a = 10.511Å, b = 13.87Å, c = 19.93Å and β = 98.17°and C2/c for 7 with a = 19.90Å, b = 10.94Å, c = 8.490Å and β = 96.74°. The fact that the aqua species 7 could be isolated after dissolving 6 in a water/acetone solution confirmed the theory of many Ru(III) complexes being initially transformed, under physiological conditions, into aqua complexes in a first and often rate-determining hydrolysis step. Compounds 1 and ICR are potent **antitumor** agents which exhibit activity against a variety of **tumor** cells and experimental **tumor** models in animals, including autochthonous colorectal **tumors**. Clinical studies with 1 are in preparation.

CT Medical Descriptors:
***antineoplastic activity**
animal experiment
animal tissue
article
chemical reaction kinetics
chemical structure
colorectal tumor
controlled study
crystal structure
drug hydrolysis
drug stability
high performance liquid chromatography
infrared spectroscopy
nonhuman
nuclear magnetic resonance spectroscopy
rat
reaction analysis
tumor volume
ultraviolet spectroscopy
X ray crystallography
Drug Descriptors:
***antineoplastic agent: AN, drug analysis**
***antineoplastic agent: CM, drug comparison**
***antineoplastic agent: DV, drug development**
*ruthenium complex: AN, drug analysis
*ruthenium complex: CM, drug comparison
*ruthenium complex: DV, drug development
cisplatin: CM, drug comparison
cisplatin: PD, pharmacology
fluorouracil: CM, drug comparison
fluorouracil: PD, pharmacology
indazolium tetrachlorobis(indazole)ruthenate: CM, drug comparison
indazolium tetrachlorobis(indazole)ruthenate: DV, drug development
unclassified drug

RN (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (fluorouracil) 51-21-8

L90 ANSWER 6 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 95348179 EMBASE
DN 1995348179
TI Hlnd(Rulnd2Cl4), KP-692, **KP-1019** (anhydrous).
SO Drugs of the Future, (1995) Vol. 20, No. 10, pp. 1060.
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)

FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
ED Entered STN: 951228
Last Updated on STN: 951228
CT Medical Descriptors:
***antineoplastic activity**
human
human cell
short survey
tumor cell
Drug Descriptors:
***antineoplastic agent: PD, pharmacology**
*metal complex: PD, pharmacology
*ruthenium complex: PD, pharmacology
indazolium tetrachlorobis(indazole)ruthenate: PD, pharmacology
unclassified drug
CN Kp 692; **Kp 1019**

L90 ANSWER 7 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 94361620 EMBASE
DN 1994361620
TI HInd(RuInd2Cl4). KP-692. IndH(RuInd2Cl4). **KP-1019** (anhydrous).
SO Drugs of the Future, (1994) Vol. 19, No. 10, pp. 952-953.
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
ED Entered STN: 950105
Last Updated on STN: 950105
CT Medical Descriptors:
***colon cancer: DT, drug therapy**
*leukemia p 388
*sarcoma 180
animal model
drug protein binding
nonhuman
rat
short survey
Drug Descriptors:
***antineoplastic agent: PD, pharmacology**
***antineoplastic agent: DT, drug therapy**
*ruthenium complex: PD, pharmacology
*ruthenium complex: DT, drug therapy
indazolium tetrachlorobis(indazole)ruthenate: PD, pharmacology
indazolium tetrachlorobis(indazole)ruthenate: DT, drug therapy
unclassified drug
CN Kp 692; **Kp 1019**

L90 ANSWER 8 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 93009429 EMBASE
DN 1993009429
TI Hind(Rulnd2Cl4). KP-692. IndH(Rulnd2Cl4).

SO Drugs of the Future, (1992) Vol. 17, No. 10, pp. 957.
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
ED Entered STN: 930207
Last Updated on STN: 930207
CT Medical Descriptors:
*dna damage
***ovary cancer**
human
human cell
short survey
Drug Descriptors:
***antineoplastic agent: PD, pharmacology**
***antineoplastic agent: CM, drug comparison**
*metal complex: PD, pharmacology
*metal complex: CM, drug comparison
*ruthenium complex: PD, pharmacology
*ruthenium complex: CM, drug comparison
budotitane: PD, pharmacology
budotitane: CM, drug comparison
cisplatin: PD, pharmacology
cisplatin: CM, drug comparison
indazolium tetrachlorobis(indazole)ruthenate: PD, pharmacology
indazolium tetrachlorobis(indazole)ruthenate: CM, drug comparison
unclassified drug
RN (budotitane) 85969-07-9; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2
CN Kp 692

L90 ANSWER 9 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 91240646 EMBASE
DN 1991240646
TI New platinum, titanium, and ruthenium complexes with different patterns of DNA damage in rat ovarian **tumor** cells.
AU Fruhauf S.; Zeller W.J.
CS Inst. Toxicology/Chemotherapy, German Cancer Research Center,6900 Heidelberg, Germany
SO Cancer Research, (1991) Vol. 51, No. 11, pp. 2943-2948.
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 911216
Last Updated on STN: 911216
AB DNA protein cross-links (DPC), DNA interstrand cross-links (ISCL), and DNA single strand breaks following treatment of experimental ovarian **tumor** cells (O-342) with five new metal complexes (three platinum, one titanium, one ruthenium compounds) were investigated at 6, 24, and 48 h after drug exposure and compared with their in vitro growth inhibitory potential. cis-Diamminedichloroplatinum(II) (cisplatin, DDP) served as reference drug. The following new compounds were tested:

18-crown-6-tetracarboxybis-diammineplatinum(II) (CTDP), cis-aminotris-methylenephosphonato-diammineplatinum(II) (AMDP), cis-diamminecyclohexano-aminotrismethylenephosphonato-platinum(II) (DAMP), diethoxybis-(1-phenylbutane-1,3-dionato)-titanium(IV) (budotitane), and trans-indazolium-tetrachlorobisindazole-ruthenate(III) (IndCR). At equimolar concentrations DNA cross-linking activity of the platinum agents decreased in the order cisplatin, CTDP, AMDP, DAMP; this was paralleled by growth inhibition in a cell proliferation assay. CTDP-induced interstrand cross-linking occurred more slowly compared to cisplatin (DDP) (6 h: CTDP, 73 ± 15 versus DDP, 365 ± 72 rad equivalents), but reached a peak similar to cisplatin 24 h after exposure (CTDP, 317 ± 68 versus DDP, 392 ± 116 rad equivalents). At this time point in contrast to DDP no DNA protein cross-links were observed for CTDP (total cross-links: CTDP 310 ± 71, DDP 1987 ± 436 rad equivalents). Thus, at 24 h, CTDP was found to be distinctly less reactive to proteins than DDP, and it is suggested that CTDP might be similar in its toxicity pattern to the structurally related compound carboplatin which was also reported to be less reactive to protein than DDP. By 48 h, CTDP- and DDP-induced interstrand cross-links were 65 ± 21 and 180 ± 33 rad equivalents, respectively. Although at a lower level, by 24 h, AMDP showed a ratio of ISCL to total cross-links (179 ± 39 versus 213 ± 31 rad equivalents), which was comparable to CTDP. The second biphosphonate complex DAMP was the least active platinum compound in terms of DNA damage, effecting only 16 ± 7 rad equivalents ISCL and 63 ± 23 rad equivalents total cross-links; similar to DDP, DAMP displayed a higher DPC fraction at 24 h. The titanium complex diethoxybis-(1-phenylbutane-1,3-dionato)-tita-nium(IV) showed dose-dependent inhibition of cell proliferation, while no significant DNA damage could be detected with the alkaline elution technique. These results, together with observations from other authors, indicating that space-filling planar aromatic ring systems are important for its **antitumor** activity, suggest as possible mechanism of action of diethoxybis-(1-phenylbutane-1,3-dionato)-titanium(IV) intercalation into the DNA. Following administration of the ruthenium compound IndCR only few ISCL and DPC were observed with a maximum at 6 h (ISCL, 15 ± 5; total cross-links, 49 ± 14 rad equivalents); thereafter both lesions were declining. Further studies on the mechanisms of action of this class of **antitumor** agents should take into account that in hypoxic **tumor** tissue the Ru(III)-ion of IndCR might be reduced to Ru(II) which is known to be more reactive to DNA.

CT Medical Descriptors:
***cancer cell**
*dna damage
***ovary tumor: TH, therapy**
***ovary tumor: DT, drug therapy**
animal experiment
animal tissue
article
female
mouse
nonhuman
priority journal
Drug Descriptors:
*metal complex: AN, drug analysis
*metal complex: PD, pharmacology
*metal complex: TO, drug toxicity
*metal complex: CM, drug comparison
*metal complex: DV, drug development
*platinum complex: AN, drug analysis
*platinum complex: DV, drug development

*platinum complex: CM, drug comparison
*platinum complex: TO, drug toxicity
*platinum complex: PD, pharmacology
*ruthenium complex: CM, drug comparison
*ruthenium complex: DV, drug development
*ruthenium complex: AN, drug analysis
*ruthenium complex: PD, pharmacology
*ruthenium complex: TO, drug toxicity
18 crown 6 tetracarboxybis(diammineplatinum): DV, drug development
18 crown 6 tetracarboxybis(diammineplatinum): PD, pharmacology
18 crown 6 tetracarboxybis(diammineplatinum): CM, drug comparison
18 crown 6 tetracarboxybis(diammineplatinum): TO, drug toxicity
18 crown 6 tetracarboxybis(diammineplatinum): AN, drug analysis
budotitane: CM, drug comparison
budotitane: DV, drug development
budotitane: AN, drug analysis
budotitane: PD, pharmacology
budotitane: TO, drug toxicity
cis aminotrismethylenephosphonatodiammineplatinum: CM, drug comparison
cis aminotrismethylenephosphonatodiammineplatinum: TO, drug toxicity
cis aminotrismethylenephosphonatodiammineplatinum: PD, pharmacology
cis aminotrismethylenephosphonatodiammineplatinum: AN, drug analysis
cis aminotrismethylenephosphonatodiammineplatinum: DV, drug development
cis diamminecyclohexanoaminotrismethylenephosphatoplatinum: PD, pharmacology
cis diamminecyclohexanoaminotrismethylenephosphatoplatinum: TO, drug toxicity
cis diamminecyclohexanoaminotrismethylenephosphatoplatinum: AN, drug analysis
cis diamminecyclohexanoaminotrismethylenephosphatoplatinum: CM, drug comparison
cis diamminecyclohexanoaminotrismethylenephosphatoplatinum: DV, drug development
cisplatin: CM, drug comparison
indazolium tetrachlorobis(indazole)ruthenate: TO, drug toxicity
indazolium tetrachlorobis(indazole)ruthenate: PD, pharmacology
indazolium tetrachlorobis(indazole)ruthenate: AN, drug analysis
indazolium tetrachlorobis(indazole)ruthenate: DV, drug development
indazolium tetrachlorobis(indazole)ruthenate: CM, drug comparison
titanium complex: TO, drug toxicity
titanium complex: PD, pharmacology
titanium complex: AN, drug analysis
titanium complex: DV, drug development
titanium complex: CM, drug comparison
unclassified drug

RN (budotitane) 85969-07-9; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2
CO Behringwerke (Germany)

L90 ANSWER 10 OF 12 EMBASE
AN 92006337 EMBASE
DN 1992006337
TI Hlnd(Rulnd2Cl4), IndH(Rulnd2Cl4), KP1692.
SO Drugs of the Future, (1991) Vol. 16, No. 10, pp. 959.
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index

LA English
ED Entered STN: 920320
Last Updated on STN: 920320
CT Medical Descriptors:
***antineoplastic activity**
***colon cancer**
cell culture
human
human cell
short survey
tumor cell
Drug Descriptors:
***antineoplastic agent: PD, pharmacology**
***antineoplastic agent: CM, drug comparison**
*metal complex: PD, pharmacology
*metal complex: CM, drug comparison
*ruthenium complex: PD, pharmacology
*ruthenium complex: CM, drug comparison
dinaline: CM, drug comparison
indazolium tetrachlorobis(indazole)ruthenate: PD, pharmacology
indazolium tetrachlorobis(indazole)ruthenate: CM, drug comparison
unclassified drug
RN (dinaline) 58338-59-3

L90 ANSWER 11 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 91111671 EMBASE
DN 1991111671
TI In vitro evaluation of platinum, titanium and ruthenium metal complexes in cisplatin-sensitive and -resistant rat ovarian **tumors**.
AU Fruhauf S.; Zeller W.J.
CS Institute of Toxicology, and Chemotherapy, German Cancer Research Cent., Im Neuenheimer Feld 280,W-6900 Heidelberg, Germany
SO Cancer Chemotherapy and Pharmacology, (1991) Vol. 27, No. 4, pp. 301-307. ISSN: 0344-5704 CODEN: CCPHDZ
CY Germany
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 911216
Last Updated on STN: 911216
AB The **antitumor** activity of eight new metal complexes (three platinum, one titanium, four ruthenium derivatives) was investigated in a cisplatin (DDP)-sensitive (O-342) and a DDP-resistant (O-342/DDP) ovarian **tumor** line using the bilayer soft-agar assay. A continuous exposure set up at logarithmically spaced concentrations was used to test the drugs; to uncover possible pharmacokinetic features, a short-term exposure was additionally included for selected compounds. DDP served as the reference drug. The following compounds were investigated: 18-crown-6-tetracarboxybis-diammineplatinum(II) (CTDP), cis-aminotrismethylenephosphonato-diammineplatinum(II) (ADP), cis-diamminecyclohexano-aminotrismethylenephosphonato-platinum(II) (DAP), diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV) (DBT, budotitane), trans-imidazolium-bisimidazoletetrachlororuthenate(III) (ICR), trans-indazolium-tetrachlorobisindazoleruthenate(III) (IndCR),cis-triazolium-tetrachlorobistriazoleruthenate(III) (TCR) and

trans-pyrazolium-tetrachlorobispyrazoleruthenate(III) (PCR). Of the new metal complexes, CTDP was the most active compound in O-342, resulting in a percentage of control plating efficiency (± SE) of 1 ± 1, 12 ± 8 and 40 ± 21 following continuous exposure to 10, 1 and 0.1 μM, respectively, and was thus comparable to DDP at equimolar concentrations. In the resistant line, 10 μM CTDP reduced colony growth to 18% ± 8%, whereas an equimolar concentration of DDP effected a reduction to 26% ± 9%. During short-term exposure, CTDP was inferior to DDP, which may be ascribed to the stability of the bis-dicarboxylate platinum ring system. The titanium compound DBT, in contrast, showed promising effects at its highest concentration (100 μM) during short-term exposure in both lines; at this concentration the activity in O-342/DDP was higher than that in O-342 (7% ± 7% vs 34% ± 17% of control plating efficiency at 100 μM). All ruthenium complexes showed higher activity in the resistant line O-342/DDP than in the sensitive counterpart. ICR was the most active compound. Following continuous exposure of O-342/DDP cells to 10 μM ICR, colony growth was reduced to 18% ± 4% that of controls. Further studies should concentrate on CTDP and ICR for the following reasons: the activity of CTDP was equal to that of DDP at equimolar concentrations during continuous exposure; considering that the in vivo toxicity of DDP was 3-fold that of CTDP, an increase in the therapeutic index of CTDP would be expected. ICR showed the best effect of all ruthenium complexes; it was superior to DDP in the resistant line.

CT Medical Descriptors:

***antineoplastic activity**

***ovary tumor**

animal cell

animal experiment

article

cancer cell culture

clonogenic assay

controlled study

drug resistance

female

histology

intraperitoneal drug administration

nonhuman

priority journal

rat

Drug Descriptors:

***antineoplastic agent: PD, pharmacology**

*budotitane: PD, pharmacology

*budotitane: DV, drug development

*cisplatin: PD, pharmacology

*platinum complex: PD, pharmacology

*ruthenium complex: PD, pharmacology

18 crown 6 tetracarboxybis(diammineplatinum): PD, pharmacology

18 crown 6 tetracarboxybis(diammineplatinum): DV, drug development

ethylnitrosourea: TO, drug toxicity

imidazolium tetrachlorobis(imidazole)ruthenate: DV, drug development

imidazolium tetrachlorobis(imidazole)ruthenate: PD, pharmacology

indazolium tetrachlorobis(indazole)ruthenate: DV, drug development

indazolium tetrachlorobis(indazole)ruthenate: PD, pharmacology

nitrilotrimethylenephosphonato diammineplatinum (ii): PD, pharmacology

nitrilotrimethylenephosphonato diammineplatinum (ii): DV, drug development

platinum 1,2 diaminocyclohexane nitrilotrimethylenephosphonate: PD, pharmacology

platinum 1,2 diaminocyclohexane nitrilotrimethylenephosphonate: DV, drug development

pyrazolium tetrachlorobis(pyrazole) ruthenate: PD, pharmacology

pyrazolium tetrachlorobis(pyrazole) ruthenate: DV, drug development
triazolium bis(triazole)tetrachlororuthenate: PD, pharmacology
triazolium bis(triazole)tetrachlororuthenate: DV, drug development
unclassified drug
RN (budotitane) 85969-07-9; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (ethylnitrosourea) 759-73-9
CO Behringwerke (Germany)

L90 ANSWER 12 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 91010053 EMBASE
DN 1991010053
TI Hlnd(Rulnd2Cl4).
AU Berger M.R.; Galeano A.; Seelig M.; **Keppler B.K.**
CS Institute of Toxicology and Chemotherapy, German Cancer Research Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, Germany
SO Drugs of the Future, (1990) Vol. 15, No. 10, pp. 992-994.
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
ED Entered STN: 911216
Last Updated on STN: 911216
CT Medical Descriptors:
***colorectal cancer**
*drug screening
*drug synthesis
***tumor cell**
animal cell
animal model
intraperitoneal drug administration
intravenous drug administration
nonhuman
peritonitis
rat
short survey
solid tumor
Drug Descriptors:
***antineoplastic metal complex: TO, drug toxicity**
***antineoplastic metal complex: DO, drug dose**
***antineoplastic metal complex: CM, drug comparison**
***antineoplastic metal complex: AD, drug administration**
***antineoplastic metal complex: AN, drug analysis**
***antineoplastic metal complex: DV, drug development**
indazolium tetrachlorobis(indazole)ruthenate: TO, drug toxicity
indazolium tetrachlorobis(indazole)ruthenate: DO, drug dose
indazolium tetrachlorobis(indazole)ruthenate: CM, drug comparison
indazolium tetrachlorobis(indazole)ruthenate: AD, drug administration
indazolium tetrachlorobis(indazole)ruthenate: AN, drug analysis
indazolium tetrachlorobis(indazole)ruthenate: DV, drug development
unclassified drug
CN Kp 692

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FILE LAST UPDATED: 6 Dec 2005 (20051206/ED)

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L77 ANSWER 1 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:575093 HCAPLUS
DN 137:119658
TI Compositions containing a ruthenium(III) complex and a heterocycle and their screening for cytotoxicity
IN **Keppler, Bernhard**
PA **Faustus Forschungs Cie., Germany**
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002059135	A1	20020801	WO 2002-EP863	20020128 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	CA 2436260	AA	20020801	CA 2002-2436260	20020128 <--
	EP 1353932	A1	20031022	EP 2002-734844	20020128 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004528292	T2	20040916	JP 2002-559437	20020128 <--
	US 2005032801	A1	20050210	US 2003-627519	20030725 <--
PRAI	DE 2001-10103565	A	20010126 <--		
	WO 2002-EP863	W	20020128 <--		

OS MARPAT 137:119658

AB The invention relates to compns. containing a ruthenium (III) complex and a heterocycle, a method for the production thereof, a pharmaceutical containing said compns. and a kit. The invention also relates to a composition (A) which can be obtained by reacting a compound of general formula M3-n-p-2pr[RuX6-n-p-2rBn(H2O)p(OH)q(O)r]2r+1, with a compound of general formula B'(HX')s. The invention further relates to a composition (B) which can be obtained by mixing a compound of general formula (B'H)3-n-p-2pr[RuX6-n-p-2rBn(H2O)p(OH)q(O)r]2r+1 with a compound of general formula MX'. Thus sodium trans-[RuCl4(und)2] (KP1339) was reacted with indazolium hydrochloride; the formed products were trans[tetrachlorobis(1H-indazole)ruthenate] (**KP1019**) and sodium chloride. Cytotoxicity screenings showed, that **KP1019** is less effective than KP1339; the 1:1 mixture of KP1339 and indazolium is as effective as KP1339 sep. Increasing the ratio of indazolium in the KP1339 - indazolium composition increased the cytotoxicity.

IT **197723-00-5**, KP 1339
RL: **PAC (Pharmacological activity)**; RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(compns. containing a ruthenium(III) complex and a heterocycle)

RN 197723-00-5 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, sodium, (OC-6-11)-(9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **124875-20-3P, KP 1019**
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(compns. containing a ruthenium(III) complex and a heterocycle)

RN 124875-20-3 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

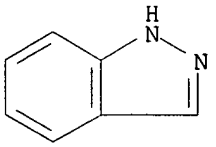
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



RETABLE

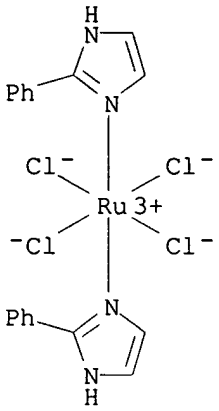
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Depenbrock, H	1997	33	2404	EUROPEAN JOURNAL OF	HCAPLUS
Galeano, A	1992	42	821	ARZNEIM-FORSCH	HCAPLUS
Garzon, F	1987	19	347	CANCER CHEMOTHER PHA	HCAPLUS
Gopal, Y	2001	26	271	JOURNAL OF BIOSCIENC	HCAPLUS
Keller, H	1989			US 4843069 A	HCAPLUS
Keppler, B	1997			WO 9736595 A	HCAPLUS
Keppler, B	1989	10	41	PROG CLIN BIOCHEM ME	HCAPLUS
Kratz, F	1994	1	169	MET-BASED DRUGS	HCAPLUS
Kratz, F	1996	3	15	MET-BASED DRUGS	HCAPLUS
Kreuser, E	1992	19	73	SEMIN ONCOL	
Pacor, S	1990		482	MET IONS BIOL MED, P	HCAPLUS

L77 ANSWER 2 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:761387 HCAPLUS
DN 136:95695
TI Preparation, physicochemical characterization and pharmacological study of novel ruthenium(III) complexes with imidazole and benzimidazole derivatives
AU Nikolova, Antonia; Ivanov, Darvin; Buyukliev, Rossen; Konstantinov, Spiro; Karaivanova, Margarita
CS Department of Chemistry, Faculty of Pharmacy, Medical University, Sofia, Bulg.
SO Arzneimittel-Forschung (**2001**), 51(9), 758-762
CODEN: ARZNAD; ISSN: 0004-4172
PB Editio Cantor Verlag
DT Journal
LA English
AB Complex compds. of ruthenium(III) with 1,2-dimethylimidazole, 2-phenylimidazole and 2-aminobenzimidazole were prepared and were characterized by physicochem. methods. Coordination sites were determined The complexes were tested for cytotoxic activity using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) dye-reduction assay and the values LD50 were evaluated.
IT **389119-10-2P**
RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; PRP (Properties); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(physicochem. characterization and pharmacol. of ruthenium(III) complexes with imidazole and benzimidazole derivs.)
RN 389119-10-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2-phenyl-1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 2-phenyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

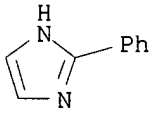
CRN 389119-09-9
CMF C18 H16 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 670-96-2
CMF C9 H8 N2



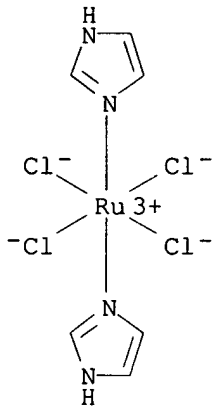
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ayres, H	1950	22	1277	Anal Chem	
Clarke, M	1980		157	ACS Simposium Series	
Clarke, M	1980	11	231	Metal Ions in Biolog	HCAPLUS
Cordes, M	1968	24A	1421	Spectrochim Acta	
Cordes, M	1968	24A	237	Spectrochim Acta	
Dwyer, F	1965	19	195	Br J Cancer	HCAPLUS
Garzon, F	1987	19	347	Cancer Chemother Pha	HCAPLUS
Geary, W	1971	7	113	Coord Chem Rev	
Keppler, B	1987	37	770	Arzneim-Forsch/Drug	
Keppler, B	1986	111	166	Cancer Res Clin Onco	HCAPLUS
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1987	26	844	Inorg Chem	HCAPLUS
Lippincott, E	1958	10	307	Spectrochim Acta	HCAPLUS
Mestroni, G	1987	137	63	Inorg Chim Acta	HCAPLUS
Mosmann, T	1983	65	55	J Immunol Methods	MEDLINE
Nikolova, A	1998	45	12	Pharmacia	
Otting, W	1956	89	2887	Chem Ber	HCAPLUS
Sava, G	1987	137	69	Inorg Chim Acta	HCAPLUS
Van den Heuvel, M	1987	6	279	Hum Toxicol	MEDLINE
Yasbin, R	1980	31	355	Chem Biol Interact	HCAPLUS

L77 ANSWER 3 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:547785 HCAPLUS
DN 136:256819
TI Topoisomerase II poisoning by indazole and imidazole complexes of ruthenium
AU Gopal, Y. N. Vashisht; Kondapi, Anand K.
CS Department of Biochemistry, University of Hyderabad, Hyderabad, 500 044, India
SO Journal of Biosciences (Bangalore, India) (**2001**), 26(2), 271-276
CODEN: JOBSDN; ISSN: 0250-5991
PB Indian Academy of Sciences
DT Journal
LA English
AB Trans-imidazolium (bis imidazole) tetrachloro ruthenate (RuIm) and trans-indazolium (bis indazole) tetrachloro ruthenate (RuInd) are ruthenium coordination complexes, which were first synthesized and exploited for their anticancer activity. These mols. constitute two of the few most effective anticancer ruthenium compds. The clin. use of these compds. however was hindered due to toxic side effects on the human body. Our present study on topoisomerase II poisoning by these compds. shows that they effectively poison the activity of topoisomerase II by forming a ternary cleavage complex of DNA, drug and topoisomerase II. The thymidine incorporation assays show that the inhibition of cancer cell proliferation correlates with topoisomerase II poisoning. The present study on topoisomerase II poisoning by these two compds. opens a new avenue for renewing further research on these compds. This is because they could be effective lead candidates for the development of more potent and less toxic ruthenium containing topoisomerase II poisons. Specificity of action on this mol. target may reduce the toxic effects of these ruthenium-containing mols. and thus improve their therapeutic index.
IT **103875-27-0 142388-45-2**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(topoisomerase II poisoning by indazole and imidazole complexes of ruthenium)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

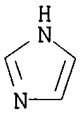
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

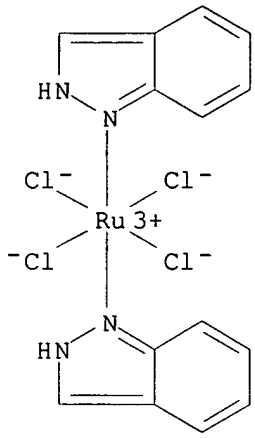
CRN 288-32-4
CMF C3 H4 N2



RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

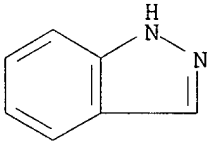
CRN 142388-44-1
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



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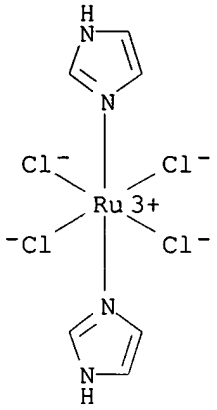
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adachi, Y	1991	64	137	Cell	HCAPLUS
Berger, J	1996	379	225	Nature (London)	HCAPLUS
Bradford	1976	72	248	Anal Biochem	HCAPLUS
Downes, C	1994	372	467	Nature (London)	HCAPLUS
Froelich-Ammon, S	1995	270	21429	J Biol Chem	HCAPLUS
Fruhauf, S	1991	51	2943	Cancer Res	MEDLINE
Galande, S	1996	1308	58	Biochem Biophys Acta	HCAPLUS
Jayaraju, D	1999	369	68	Arch Biochem Biophys	HCAPLUS
Keppler, B	1990	17	261	Cancer Treat Rev	HCAPLUS
Keppler, B	1989	10	41	Prog Clin Biochem Me	HCAPLUS
Ni Dhubhghaill, O	1994		3305	J Chem Soc Dalton Tr	HCAPLUS
Osheroff, N	1983	258	9536	J Biol Chem	HCAPLUS
Pruss, G	1986	83	8952	Proc Natl Acad Sci U	HCAPLUS
Vashisht Gopal, Y	2000	376	229	Arch Biochem Biophys	HCAPLUS
Vashisht Gopal, Y	1999	38	4382	Biochemistry	
Wang, J	1985	54	665	Annu Rev Biochem	MEDLINE
Wang, J	1996	65	635	Annu Rev Biochem	HCAPLUS
Wang, J	1991	266	6659	J Biol Chem	HCAPLUS
Wang, Z	1994	16	460	BioTechniques	HCAPLUS

Watt, P	1994	303	681	Biochem J	HCAPLUS
Zecheidrich, E	1989	28	6229	Biochemistry	

L77 ANSWER 4 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:467186 HCAPLUS
DN 135:313268
TI Investigations into the interaction between tumor-inhibiting ruthenium(III) complexes and nucleotides by capillary electrophoresis
AU Kung, A.; Pieper, T.; **Keppler, B. K.**
CS Institute of Inorganic Chemistry, University of Vienna, Vienna, A-1090, Austria
SO Journal of Chromatography, B: Biomedical Sciences and Applications (**2001**), 759(1), 81-89
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier Science B.V.
DT Journal
LA English
AB Ruthenium(III) complexes of the general formula HL[RuCl4L2], with two trans-standing heterocyclic ligands L bound to ruthenium via nitrogen, show remarkable activity in different tumor models. To obtain a deeper insight into the mode of action of this class of anticancer compds., we investigated the interaction of HIm trans-[RuCl4(i.m.)2] (i.m., imidazole) and HInd trans-[RuCl4(ind)2] (ind, indazole) with all four nucleoside monophosphates in buffered solution by means of capillary electrophoresis. A preference for GMP- and AMP-coordination was found. A decrease of the pH resulted in a significantly increased amount of bound nucleotide. This feature seems to be interesting with regard to the lower pH values in solid tumors.
IT **103875-27-0 124875-20-3 189556-38-5**
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(use of capillary electrophoresis in studying interaction between tumor-inhibiting ruthenium(III) complexes and nucleotides)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

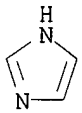
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

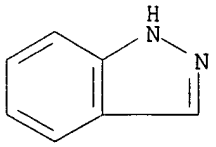
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



RN 189556-38-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessic, E	1993	203	205	Inorg Chim Acta	
Alessio, E	1989	111	7068	J Am Chem Soc	HCAPLUS
Cauci, S	1987	137	19	Inorg Chim Acta	HCAPLUS
Cauci, S	1991	43	739	J Inorg Biochem	HCAPLUS
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Chottard, J	1980	102	5565	J Am Chem Soc	HCAPLUS
Eastman, A	1987	34	155	Pharmacol Ther	HCAPLUS
Esposito, G	1992	31	7094	Biochemistry	HCAPLUS
Fichtinger-Schepman, A	1985	24	707	Biochemistry	HCAPLUS
Fichtinger-Schepman, A	1982	10	5345	Nucl Acids Res	HCAPLUS
Hartmann, M	1998	267	137	Inorg Chim Acta	HCAPLUS
Jamieson, E	1999	99	2467	Chem Rev	HCAPLUS
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Kung, A	2001	6	292	J Biol Inorg Chem	HCAPLUS
Lipponer, K	1996	3	243	Metal-Based Drugs	HCAPLUS
Mestroni, G	1993	1	41	Metal-Based Drugs	
Mestroni, G	1989	10	72	Prog Clin Biochem Me	
Nidhubhghaill, O	1994		3305	J Chem Soc Dalton Tr	HCAPLUS
Raudaschl-Sieber, G	1985	107	3591	J Am Chem Soc	HCAPLUS
Scovell, W	1977	99	120	J Am Chem Soc	HCAPLUS
Seelig, M	1990		476	Metal Ions in Biolog	HCAPLUS
Siegel, H	1994	116	2958	J Am Chem Soc	
Tullius, T	1982	103	4620	J Am Chem Soc	
Tullius, T	1982	103	4620	J Am Chem Soc	
Vilaplana, R	1995	2	211	Metal-Based Drugs	HCAPLUS
Zenker, A	1999	852	337	J Chrom A	HCAPLUS

L77 ANSWER 5 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:396171 HCAPLUS
DN 135:204910
TI Biophysical analysis of natural, double-helical DNA modified by anticancer heterocyclic complexes of ruthenium(III) in cell-free media
AU Malina, Jaroslav; Novakova, Olga; **Keppler, Bernhard K.**; Alessio, Enzo; Brabec, Viktor
CS Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, 61265, Czech Rep.
SO JBIC, Journal of Biological Inorganic Chemistry (**2001**), 6(4), 435-445
CODEN: JJBCFA; ISSN: 0949-8257
PB Springer-Verlag
DT Journal
LA English
AB Modifications of natural DNA by three anticancer heterocyclic ruthenium(III) compds. were studied by methods of mol. biophysics. These methods included DNA binding studies using atomic absorption spectrophotometry, inhibition of restriction endonucleases, mapping of DNA adducts by transcription assay, interstrand crosslinking employing gel electrophoresis under denaturing conditions, DNA unwinding studied by gel electrophoresis, CD anal. of the B→Z transition in DNA, and DNA melting curves measured by absorption spectrophotometry. The results

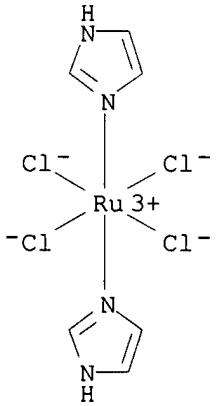
indicate that the complexes HIm[trans-Cl4Im2RuIII], HInd[trans-Cl4Ind2RuIII], and Na[trans-Cl4Im(Me2SO)RuIII] (Im and Ind stand for imidazole and indazole, resp.) coordinate irreversibly to DNA. Their DNA binding mode is, however, different from that of cisplatin. Interestingly, Na[trans-Cl4Im(Me2SO)RuIII] binds to DNA considerably faster than the other two ruthenium compds. and cisplatin. In addition, when Na[trans-Cl4Im(Me2SO)RuIII] binds to DNA it exhibits an enhanced base sequence specificity in comparison with the other two ruthenium complexes. Na[trans-Cl4Im(Me2SO)RuIII] also forms bifunctional intrastrand adducts on double-helical DNA which are capable of terminating RNA synthesis in vitro, while the capability of the other two ruthenium compds. to form such adducts is markedly lower. This observation has been interpreted to mean that the bifunctional adducts of HInd[trans-Cl4Ind2RuIII] and Na[trans-Cl4Im2RuIII] formed on rigid double-helical DNA are sterically more crowded by their octahedral geometry than those of Na[trans-Cl4Im(Me2SO)RuIII]. In addition, the adducts of all three ruthenium compds. affect the conformation of DNA, Na[trans-Cl4Im(Me2SO)RuIII] being most effective. It has been suggested that the altered DNA binding mode of ruthenium compds. in comparison with cisplatin might be an important factor responsible for the altered cytostatic activity of this class of ruthenium compds. in tumor cells.

IT **103875-27-0 124875-20-3**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(anal. of natural, double-helical DNA modified by anticancer heterocyclic complexes of ruthenium(III) in cell-free media)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

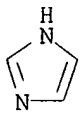
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

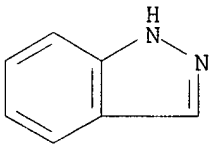
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Barca, A	1999	423	171	Mutation Res	HCAPLUS
Bellon, S	1991	30	8026	Biochemistry	HCAPLUS
Brabec, V	1976	4	76	Biophys Chem	
Brabec, V	1970	6	290	Biophysik	HCAPLUS
Brabec, V	1993	90	5345	Proc Natl Acad Sci U	HCAPLUS
Clarke, M	1999	99	2511	Chem Rev	HCAPLUS
Clarke, M	1993		129	Metal complexes in c	HCAPLUS
Cleare, M	1974	12	349	Coord Chem Rev	HCAPLUS
Cleare, M	1977	7	1	J Clin Hematol Oncol	HCAPLUS
Cocchietto, M	2000	20	197	Anticancer Res	HCAPLUS
Eastman, A	1987	34	155	Pharmacol Ther	HCAPLUS
Farrell, N	1990	29	9522	Biochemistry	HCAPLUS
Farrell, N	1996	32	603	Metal ions in biolog	HCAPLUS
Farrell, N	2000		321	Platinum based drugs	HCAPLUS
Fichtinger-Schepman, A	1985	24	707	Biochemistry	HCAPLUS
Frasca, D	1996	3	197	J Met-Based Drugs	HCAPLUS
Gallori, E	2000	376	156	Arch Biochem Biophys	HCAPLUS

Jamieson, E	1999	99	2467	Chem Rev	HCAPLUS
Johnson, N	1989	10	1	Prog Clin Biochem Me	HCAPLUS
Kasparkova, J	1999	38	10997	Biochemistry	HCAPLUS
Keck, M	1992	114	3386	J Am Chem Soc	HCAPLUS
Keppler, B	1993			Metal complexes in c	
Keppler, B	1993		187	Metal complexes in c	HCAPLUS
Lemaire, M	1991	88	1982	Proc Natl Acad Sci U	HCAPLUS
McGregor, T	1999	77	43	J Inorg Biochem	HCAPLUS
Ni Dhubghghaill, O	1994		3305	J Chem Soc Dalton Tr	
O'Dwyer, P	1999		31	Cisplatin. Chemistry	HCAPLUS
Perez-Martin, J	1993	268	24774	J Biol Chem	HCAPLUS
Peticolas, W	1985		497	Structure and motion	HCAPLUS
Prenzler, P	1997	68	279	J Inorg Biochem	HCAPLUS
Rahmouni, A	1985	3	363	J Biomol Struct Dyn	HCAPLUS
Rosenberg, B	1999		3	Cisplatin. Chemistry	
Sava, G	1999	10	129	Anti-Cancer Drugs	HCAPLUS
Sava, G	1994	8	150	Drug Invest	HCAPLUS
Sava, G	2000	17	353	Int J Oncol	HCAPLUS
Sava, G	1999	1	143	Topics in biological	HCAPLUS
Seelig, M	1992	118	195	J Cancer Res Clin On	HCAPLUS
Ushay, H	1982	10	3573	Nucleic Acids Res	HCAPLUS
Vrana, O	1996	24	3918	Nucleic Acids Res	HCAPLUS
Wong, E	1999	99	2451	Chem Rev	HCAPLUS
Zaludova, R	1997	12	295	Anti-Cancer Drug Des	HCAPLUS
Zaludova, R	1996	60	135	Biophys Chem	HCAPLUS
Zaludova, R	1997	246	508	Eur J Biochem	HCAPLUS
Zamble, D	1996	35	10004	Biochemistry	HCAPLUS
Zamble, D	1999		73	Cisplatin. Chemistry	HCAPLUS

L77 ANSWER 6 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:354732 HCAPLUS
DN 135:220621
TI Binding of antitumor ruthenium(III) complexes to plasma proteins
AU Messori, L.; Vilchez, F. Gonzales; Vilaplana, R.; Piccioli, F.; Alessio, E.; **Keppler, B.**
CS Department of Chemistry, University of Florence, Florence, I-50121, Italy
SO Metal-Based Drugs (**2000**), 7(6), 335-342
CODEN: MBADEI; ISSN: 0793-0291
PB Freund Publishing House Ltd.
DT Journal
LA English
AB Presently, there is large interest in analyzing the interactions in vitro with plasma proteins of some novel antitumor ruthenium(III) complexes that are in preclin. or clin. phase. The joint application of separation and spectroscopic techniques provides valuable information on the nature and the properties of the resulting ruthenium/protein adducts. Recent work carried out in our laboratory points out that, under physiol. conditions, some selected ruthenium(III) complexes bind plasma proteins tightly with a marked preference for surface imidazole groups. Representative examples of interactions of antitumor ruthenium(III) complexes with plasma proteins such as albumin and transferrin are given. Notably the antitumor ruthenium(III) complexes considered here bind proteins much tighter than DNA; it is proposed that protein binding of ruthenium(III) complexes will have a large impact on the biodistribution, the pharmacokinetics and the mechanism of action of these exptl. drugs.
IT **103875-27-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(binding of antitumor ruthenium(III) complexes to plasma proteins)
RN 103875-27-0 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 103875-26-9
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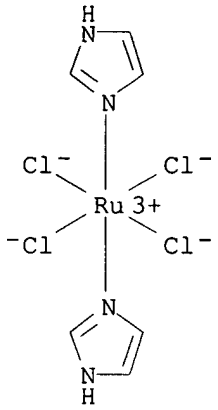
CCI CCS



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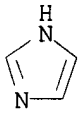
CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Anon	1999			Cisplatin	
Anon	1993			Metal Complexes in C	
Anon				Unpublished results	
Clarke, M	1999	99	2511	Chem Rev	HCAPLUS
Guo, Z	1998	273	1	Inorg Chim Acta	
Jamieson, E	1999	99	2467	Chem Rev	HCAPLUS
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Kratz, F	1994	1	169	Metal Based Drugs	HCAPLUS
Kratz, F	1996	3	15	Metal Based Drugs	HCAPLUS
Kratz, F	1993		391	Metal Complexes in C	HCAPLUS

Messori, L	2000	267	1206	Eur J Biochem	HCAPLUS
Messori, L				Recent Research Deve	
Sava, G	1999	1	143	Topics Biological In	HCAPLUS
Szpunar, J	1999	387	135	Anal Chim Acta	HCAPLUS
Trynda-Lemiesz, L	1999	73	123	J Inorg Biochem	HCAPLUS
Trynda-Lemiesz, L	2000	78	341	J Inorg Biochem	HCAPLUS
Velders, A	1998	273	259	Inorg Chim Acta	
Vilaplana, R	1994	224	15	Inorg Chim Acta	HCAPLUS
Vilaplana, R	1995	2	211	Metal Based Drugs	HCAPLUS
Vilchez, F	1998	71	45	J Inorg Biochem	HCAPLUS

L77 ANSWER 7 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:303276 HCAPLUS
DN 135:127708
TI Hydrolysis of the tumor-inhibiting ruthenium(III) complexes trans-[RuCl4(Iim)2]- and trans-[RuCl4(ind)2]- investigated by means of HPCE and HPLC-MS
AU Kung, Angelika; Pieper, Thomas; Wissiack, Rene; Rosenberg, Erwin; **Keppler, Bernhard K.**
CS Institute of Inorganic Chemistry, University of Vienna, Vienna, 1090, Austria
SO JBIC, Journal of Biological Inorganic Chemistry (**2001**), 6(3), 292-299
CODEN: JJBCFA; ISSN: 0949-8257
PB Springer-Verlag
DT Journal
LA English
AB High performance capillary electrophoresis (HPCE) as well as HPLC-mass spectrometry (HPLC-MS) were applied to the separation, identification and quantification of the tumor-inhibiting Ru compds. trans-[RuCl4(HIm)2]- (Im = imidazole) and HInd trans-[RuCl4(ind)2]- (ind = indazole) and their hydrolysis products. The half-lives for the hydrolytic decomposition of the Ru(III) compds. were determined by monitoring the relative decrease of the original complex anion under different conditions by capillary electrophoresis. The decomposition follows pseudo-first-order kinetics. The rate consts. in H2O at 25° are 1.102 ± 0.091 + 10-5 s-1 for trans-[RuCl4(Im)2]- and 0.395 ± 0.014 + 10-5 s-1 for trans-[RuCl4(ind)2]-. About 8% of trans-[RuCl4(Im)2]- but only .apprx.2% of trans-[RuCl4(ind)2]- were hydrolyzed after 1 h at room temperature Whereas the hydrolysis rate of the imidazole complex is independent of the pH value, the indazole complex hydrolyzes much faster at higher pH. The half-life of trans-[RuCl4(ind)2]- in phosphate buffer at pH 6.0 and 37° is 5.4 h, whereas it is <0.5 h at pH 7.4. In contrast to the imidazole complex, where no dependence on the buffer system was observed, hydrolysis of the indazole complex is even faster if a buffer containing H carbonate was used. The formation of [RuCl2(H2O)2(Im)2]+ could be demonstrated by HPLC-MS measurements. In the case of the indazole complex, a release of the indazole ligands gave [RuCl4(H2O)2]-.
IT **189556-38-5**
RL: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(hydrolytic decomposition kinetics in relation to pH)
RN 189556-38-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Anderson, C	1995	73	471	Can J Chem	HCAPLUS
Catalan, J	1987	110	4105	J Am Chem Soc	
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Hohmann, H	1992	31	1090	Inorg Chem	HCAPLUS
Hohmann, H	1990	174	87	Inorg Chim Acta	HCAPLUS
Holler, E	1991	41	1065	Arzneim-Forsch/Drug	HCAPLUS
Howe-Grant, M	1980	11	63	Metal Ions Biol Syst	HCAPLUS
Keppler, B	1987	26	844	Inorg Chem	HCAPLUS
Keppler, B	1993		187	Metal complexes in c	HCAPLUS
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Krogh-Jespersen, K	1987	109	7025	J Am Chem Soc	HCAPLUS
Lipponer, K	1996	3	243	Metal-Based Drugs	HCAPLUS
Ni, D	1994		3305	J Chem Soc Dalton Tr	
Pacor, S	1991	78	223	Chem Biol Interact	HCAPLUS
Pinto, H	1996			Platinum and other m	
Sava, G	1992	10	273	Clin Exp Metastasis	HCAPLUS
Seelig, M	1990		476	Metal ions in biolog	HCAPLUS
Suvachittanont, S	1994	33	895	Inorg Chem	HCAPLUS
Velders, A	1998	273	259	Inorg Chim Acta	HCAPLUS
Yagil, G	1967	23	2855	Tetrahedron	HCAPLUS

L77 ANSWER 8 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:99667 HCAPLUS
DN 134:289470
TI [RuCl3ind3] and [RuCl2ind4]: two new ruthenium complexes derived from the tumor-inhibiting RuIII compound HInd (OC-6-11)-[RuCl4ind2] (ind = indazole)
AU Pieper, Thomas; Sommer, Martina; Galanski, Markus; **Keppler, Bernhard K.**; Giester, Gerald
CS Institute of Inorganic Chemistry, University of Vienna, Vienna, A-1090, Austria
SO Zeitschrift fuer Anorganische und Allgemeine Chemie (**2001**), 627(2), 261-265
CODEN: ZAACAB; ISSN: 0044-2313
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
OS CASREACT 134:289470
AB Indazolium (OC-6-11)-tetrachlorobis(indazole)ruthenate(III), HInd (OC-6-11)-[RuCl4ind2], exhibits excellent results in different tumor models in vitro and in vivo. Substitution reactions of this Ru(III) complex are of special interest for a deeper understanding of its interactions with biol. occurring targets and its mode of action. The indazolium complex salt can be transformed to the neutral, meridionally configurated trisindazole complex (OC-6-21)-[RuCl3ind3] in solvents like THF. The x-ray crystal structure of this complex could be solved (monoclinic space group P2(1)/n, a 12.441(3), b 10.415(3), c 21.635(4) Å, β 105.02(1)°). In spite of the paramagnetic RuIII atom most of the coordinated indazole protons could be assigned with the help of two-dimensional NMR expts. Addnl., a reduced reaction product of Hind (OC-6-11)-[RuCl4ind2] in the physiol. solubilizer 2-pyrrolidone could be isolated and the x-ray crystal structure of this RuII complex, (OC-6-12)-[RuCl2ind4], crystallized with two 2-pyrrolidones, could be solved (monoclinic space group P2(1)/n, a 12.139(2), b 10.426(2), c 14.426(3) Å, β 100.06(3)°).
IT **124875-20-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(substitution with indazole and reduction)
RN 124875-20-3 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 124875-19-0
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CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
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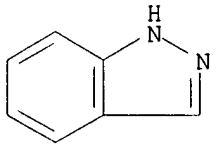

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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1997		457	Cytotoxic, Mutagenic	HCAPLUS
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Anderson, C	1995	73	471	Can J Chem	HCAPLUS
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Clarke, M	1980	12	79	J Inorg Biochem	HCAPLUS
Clarke, M	1993		129	Metal Complexes in C	HCAPLUS
Depenbrock, H	1997	33	2404	Europ J Cancer	HCAPLUS
Frasca, D	1996	3	197	Metal-Based Drugs	HCAPLUS
Galeano, A	1992	42(I)	821	Arzneimittelforschun	
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Kratz, F	1996	269	2581	J Biol Chem	
Lipponer, K	1996	3	243	Metal-Based Drugs	HCAPLUS
Mestroni, G	1993	1	41	Metal Based Drugs	
Ni Dhubhgaill, O	1994		3305	J Chem Soc, Dalton T	
Peti, W	1999		1551	Eur J Inorg Chem	HCAPLUS
Pieper, T	1997	123	S35	J Cancer Res Clin On	
Pieper, T	2000			Metal-Based Drugs in	
Sava, S	1998	16	371	Clin Exp Metastasis	
Seelig, M	1990		476	Metal Ions in Biolog	HCAPLUS
Sheldrick, G	1997			SHELXL-97, A Program	
Sheldrick, G	1997			SHELXS-97, A Program	
Smith, C	1996	1	424	J Bioinorg Chem	HCAPLUS
van Vliet, P	1995	231	57	Inorg Chim Acta	HCAPLUS
Vilaplana, R	1995	2	211	Metal Based Drugs	HCAPLUS
Wong, W	1994	C50	1406	Acta Crystallogr	HCAPLUS

L77 ANSWER 9 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:20610 HCAPLUS
DN 134:216441
TI Solvolysis of the tumor-inhibiting Ru(III)-complex trans-tetrachlorobis(indazole)ruthenate(III)
AU Pieper, Thomas; Peti, Wolfgang; **Keppler, Bernhard K.**

CS Institute of Inorganic Chemistry, University of Vienna, Vienna, A-1090, Austria
SO Metal-Based Drugs (**2000**), 7(4), 225-232
CODEN: MBADEI; ISSN: 0793-0291
PB Freund Publishing House Ltd.
DT Journal
LA English
AB Trans-[RuCl4(ind)2](Hind), with two trans indazole (ind) ligands bound to Ru via N, shows remarkable activity in different tumor models in vitro and in vivo. The solvolysis of trans-[RuCl4(ind)2]- was studied by spectroscopic techniques (UV/visible, NMR) in different solvents. The authors studied the indazolium as well as the Na salt, the latter showing improved solubility in H2O. In aqueous MeCN and EtOH the solvolysis results in one main solvento complex. The hydrolysis of the complex is more complicated and depends on the pH of the solution as well as on the buffer system.
IT **328238-75-1**
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(formation from solvolysis of tetrachlorobis(indazole)ruthenate in acetonitrile/water)
RN 328238-75-1 HCAPLUS
CN Ruthenium, aquatrichlorobis(1H-indazole-κN2)-, (OC-6-21)- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **142388-45-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(solvolysis in water and acetonitrile)
RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

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CRN 142388-44-1
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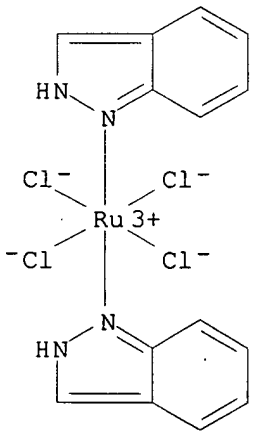
CCI CCS



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CM 2

CRN 271-44-3
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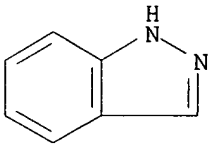

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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Anderson, C	1995	73	471	Can J Chem	HCAPLUS
Bertini, I	1986			NMR of paramagnetic	
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Clarke, M	1993		129	Metal Complexes in C	HCAPLUS
Depenbrock, H	1997	33	2404	Europ J Cancer	HCAPLUS
Galeano, A	1992	42	821	Arzneimittelforschun	
Hohmann, H	1992	31	1090	Inorg Chem	HCAPLUS
Hohmann, H	1990	174	87	Inorg Chim Acta	HCAPLUS
Holler, E	1991	41	1065	Arzneim-Forsch I Dru	HCAPLUS
Howe-Grant, M	1980	11	63	Metal Ions Biol Syst	HCAPLUS
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Lipponer, K	1996	3	243	Metal-Based Drugs	HCAPLUS
Mestroni, G	1993	1	41	Metal Based Drugs	
Ni Dhubhghaill, O	1994		3305	J Chem Soc Dalton Tr	HCAPLUS
Peti, W	1999		1551	Eur J Inorg Chem	HCAPLUS
Satterlee, J	1990	2	119	Concepts Magn Reson	HCAPLUS
Satterlee, J	1990	2	69	Concepts Magn Reson	HCAPLUS
Seelig, M	1990		476	Metal Ions in Biolog	HCAPLUS
Suvachittanont, S	1994	33	895	Inorg Chem	HCAPLUS
Velders, A	1998	273	259	Inorganica Chimica A	HCAPLUS
Vilaplana, R	1995	2	211	Metal Based Drugs	HCAPLUS

L77 ANSWER 10 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:20606 HCAPLUS
DN 134:260990
TI Biological properties of IRIM, the iridium(III) analog of (imidazolium (bisimidazole) tetrachlororuthenate) (ICR)
AU Marcon, G.; Casini, A.; Mura, P.; Messori, L.; Bergamo, A.; Orioli, P.
CS Unit of Florence, CIRCMSB, Florence, I-50121, Italy
SO Metal-Based Drugs (**2000**), 7(4), 195-200
CODEN: MBADEI; ISSN: 0793-0291
PB Freund Publishing House Ltd.
DT Journal
LA English
AB Some biol. aspects of the new complex imidazolium bisimidazole tetrachloroiridate(III) - IRIM - the iridium(III) analog of ICR, were considered. More in detail the conformational effects produced by IRIM on DNA and the cytotoxic properties of IRIM on some selected human cell lines were measured. Dialysis expts. and DNA thermal denaturation studies are

suggestive of poor binding of IRIM to DNA; formation of interstrand crosslinks is not observed In any case CD measurements suggest that addition of increasing amts. of IRIM to calf thymus DNA results into significant spectral changes, that are diagnostic of a direct interaction with DNA. A number of expts. carried out on the A2780 human ovarian carcinoma, B16 murine melanoma, MCF7 and TS mammary adenocarcinoma tumor cell lines strongly point out that IRIM does not exhibit significant growth inhibition effects within the concentration range 10-4-10-6 M. It is suggested that the lower biol. effects of IRIM compared to ICR are a consequence of the larger kinetic inertness of the iridium(III) center with respect to ruthenium(III).

IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(biol. properties of IRIM, the iridium(III) analog of (imidazolium (bisimidazole) tetrachlororuthenate) (ICR))

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

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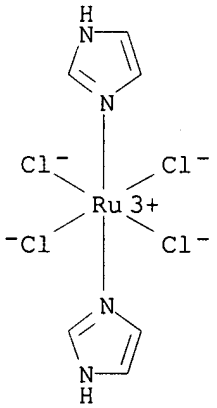
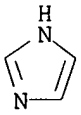
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



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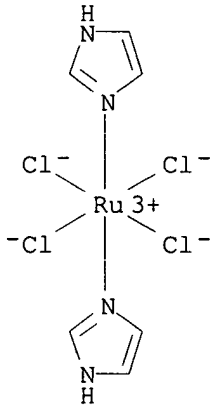
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1999	99	2201	Medicinal Inorganic	
Gallori, E	2000	376	156	Arch Biochem Biophys	HCAPLUS
Keppler, B	1993			Metal Complexes in C	
Mestroni, G	1998	273	62	Inorg Chim Acta	
Mosmann, T	1983	65	55	J Immunol Methods	MEDLINE
Mura, P	2000			Inorg Chim Acta, sub	
Sava, G	1999	1	143	Topics BioInorg Chem	HCAPLUS
Skehan, P	1990	82	1107	J Natl Cancer Inst	HCAPLUS
Wilson, W	1997		90	Methods in Molecular	

L77 ANSWER 11 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:846102 HCAPLUS
DN 134:141477
TI Lack of in vitro cytotoxicity, associated to increased G2-M cell fraction and inhibition of matrigel invasion, may predict in vivo-selective antimetastasis activity of ruthenium complexes
AU Zorzet, Sonia; Bergamo, Alberta; Cocchietto, Moreno; Sorc, Alenka; Gava, Barbara; Alessio, Enzo; Iengo, Elisabetta; Sava, Gianni
CS Department of Biomedical Sciences, Callerio Foundation-Onlus, Trieste, Italy
SO Journal of Pharmacology and Experimental Therapeutics (**2000**), 295(3), 927-933
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB The ruthenium complexes trans-dichlorotetrakisdimethylsulfoxide ruthenium(II) (trans-Ru), imidazolium trans-imidazoletetrachlororuthenate (ICR), sodium trans-tetramethylensulfoxideisoquinolinetetrachlororuthenate (TEQU), and imidazolium trans-imidazoledimethylsulfoxidetetrachlororuthena te (NAMI-A) are tested in vitro by short exposure of MCF-7, LoVo, KB, and TS/A tumor cells to 10-4 M concentration, and in vivo on Lewis lung carcinoma by a daily i.p. treatment for 6 consecutive days using equitoxic and maximum tolerated doses. NAMI-A (1) inhibited tumor cell invasion of matrigel, (2) induced a transient accumulation of cells in the G2-M phase, (3) did not modify in vitro cell growth, and (4) markedly reduced lung metastasis formation. TEQU showed significant cytotoxicity in vitro and was not antimetastatic in vivo. ICR and trans-Ru did not modify cell cycle distribution of in vitro tumor cells nor did they inhibit matrigel invasion; ICR was also devoid of antimetastasis effects in vivo. Ruthenium uptake by tumor cells did account for in vitro cytotoxicity but not for other in vitro actions or for in vivo antimetastasis activity. The contemporary absence of cytotoxicity, associated to inhibition of matrigel crossing and to transient block in the premitotic G2-M phase, appears to be prerequisites for a ruthenium compound to show in vivo-selective antimetastasis effect. The validation of this model for other classes of compds. will allow an understanding of the combined weight of the above-mentioned phenomena for tumor metastasis growth and control.

IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(lack of in vitro cytotoxicity, associated to increased G2-M cell fraction and inhibition of matrigel invasion may predict in vivo-selective antimetastasis activity of ruthenium complexes)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

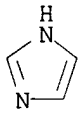
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Albini, A	1998	4	230	Pathol Oncol Res	MEDLINE
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Alessio, E	1988		617	Platinum and Other M	
Bergamo, A	1999	289	559	J Pharmacol Exp Ther	HCAPLUS

Capozzi, I	1998	113	51	Chem-Biol Interact	HCAPLUS
Clarke, M	1989		231	Metal Ions in Biolog	
Clarke, M	1988		582	Platinum and Other M	
Coluccia, M	1993	29A	1873	Eur J Cancer	HCAPLUS
Coluccia, M	1995	2	195	Metal-Based Drugs	HCAPLUS
Craciunescu, D	1987	1	229	In Vivo	HCAPLUS
Crissman, H	1973	59	766	J Cell Biol	HCAPLUS
Drewinko, B	1978	61	75	J Natl Cancer Inst	MEDLINE
Eagle, H	1959	130	432	Science (Wash DC)	HCAPLUS
Galeano, A	1992	42	821	Arzneim-Forsch	HCAPLUS
Geran, R	1972	3	13	Cancer Chemother Rep	
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1986	111	166	J Cancer Res Clin On	HCAPLUS
Kotoh, T	1999	125	536	Surgery	MEDLINE
Mestroni, G	1998			WO 98/00431	HCAPLUS
Mestroni, G	1989		71	Progress in Clinical	HCAPLUS
Mosmann, T	1983	65	55	J Immunol Methods	MEDLINE
Nagabuchi, E	1997	32	287	J Pediatr Surg	MEDLINE
Nanni, P	1983	1	373	Clin Exp Metastasis	MEDLINE
Sava, G	1999	10	129	Anticancer Drugs	HCAPLUS
Sava, G	1999	19	969	Anticancer Res	HCAPLUS
Sava, G	1995	95	109	Chem-Biol Interact	HCAPLUS
Sava, G	1998	16	371	Clin Exp Metastasis	HCAPLUS
Sava, G	1997	3	207	Curr Topics Pharmaco	HCAPLUS
Sava, G	1996	68	60	Int J Cancer	HCAPLUS
Sava, G	1989	21	617	Pharmacol Res	HCAPLUS
Sledge, G	1995	87	1546	J Natl Cancer Inst	HCAPLUS
Soule, H	1973	51	1409	J Natl Cancer Inst	MEDLINE
Tamura, H	1992	41	T13	Bunseki Kagaku	HCAPLUS
Yoneda, T	1997	99	2509	J Clin Invest	HCAPLUS

L77 ANSWER 12 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:779312 HCAPLUS
DN 134:110205
TI Effects of NAMI-A and some related ruthenium complexes on cell viability after short exposure of tumor cells
AU Bergamo, A.; Zorzet, S.; Gava, B.; Sorc, A.; Alessio, E.; Iengo, E.; Sava, G.
CS Callerio Foundation Onlus, Trieste, 34127, Italy
SO Anti-Cancer Drugs (**2000**), 11(8), 665-672
CODEN: ANTDEV; ISSN: 0959-4973
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB A series of three ruthenium complexes, i.e. trans-dichlorotetrakisdimethylsulfoxide ruthenium(II) (trans-Ru), imidazolium trans-imidazoletetrachlororuthenate (ICR) and sodium trans-tetramethylensulfoxideisoquinolinetetrachlororuthenate (TEQU), were studied in vitro in comparison to NAMI-A, a potent ruthenium-based antimetastasis agent. In vitro challenge of TS/A adenocarcinoma or KB oral carcinoma tumor cells with 10-4 M concentration for 1 h evidenced the lack of cytotoxicity of NAMI-A, ICR and trans-Ru, the accumulation of cells in the G2/M pre-mitotic cell phase by NAMI-A and the attachment of tumor cells to the plastic substrate was significantly greater for NAMI-A than for ICR. These data stress that in vitro cytotoxicity is not necessary for in vivo activity of ruthenium antitumor complexes: NAMI-A, ICR and trans-Ru, are in fact known to be active against murine tumors in the mouse system. Rather, TEQU, the compound free of in vivo activity, was the only one to reduce cell growth of in vitro cultured cells. In conclusion, the data on the effects of NAMI-A on in

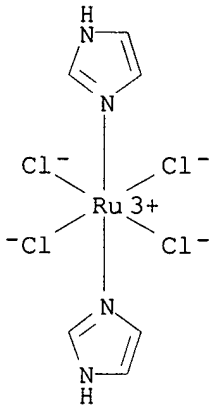
vitro cultured cells show that the increase of cell adhesion properties and the transient cell cycle arrest in the G2/M phase are much more relevant than the effects on cell properties relevant to cell growth (i.e. on CD44, CD54 or CD71 antigens) for determining in vivo antimetastasis activity.

IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effects of NAMI-A and related ruthenium complexes on cell viability after short exposure of tumor cells in relation to antimetastatic activity)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

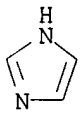
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Bergamo, A	1999	289	559	J Pharmacol Exp Ther	HCAPLUS
Capozzi, I	1998	113	51	Chem-Biol Interact	HCAPLUS
Clarke, M	1993		129	Metal complexes in c	HCAPLUS
Craciunescu, D	1987	1	229	In Vivo	HCAPLUS
Crissman, H	1973	59	766	J Cell Biol	HCAPLUS
Eagle, H	1959	130	432	Science	HCAPLUS
Galeano, A	1992	42	821	Arzneim-Forsch	HCAPLUS
Keppler, B	1990	17	261	Cancer Treat Rev	HCAPLUS
Keppler, B	1986	111	166	J Cancer Res Clin On	HCAPLUS
Mestroni, G	1989		71	Progress in clinical	HCAPLUS
Mosmann, T	1983	65	55	J Immunol Methods	MEDLINE
Nanni, P	1983	1	373	Clin Exp Metastasis	MEDLINE
Pacor, S	1999	5	110	Pathol Oncol Res	HCAPLUS
Podda, E	1998			Thesis University of	
Satoh, K	1999	80	1115	Br J Cancer	HCAPLUS
Sava, G	1995	95	109	Chem-Biol Interact	HCAPLUS
Sava, G	1998	16	371	Clin Exp Metastasis	HCAPLUS
Sava, G	1998	16	371	Clin Exp Metastasis	HCAPLUS
Sava, G	1994	8	150	Drug Invest	HCAPLUS
Sava, G	1996	68	60	Int J Cancer	HCAPLUS
Sava, G	1999		143	Topics in biological	HCAPLUS
Skehan, P	1990	82	1107	J Natl Cancer Inst	HCAPLUS

L77 ANSWER 13 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:242568 HCAPLUS
DN 133:83719
TI New anticancer agents developed by the new drug development group (AWO)
AU **Keppler, B. K.**; Eisenbrand, G.; Jakupec, M. A.
CS Institute of Inorganic Chemistry, Vienna University, Vienna, Austria
SO Contributions to Oncology (**1999**), 54(Relevance of Tumor Models for Anticancer Drug Development), 361-367
CODEN: COONEV; ISSN: 0250-3220
PB S. Karger AG
DT Journal; General Review
LA English
AB A review with 8 refs. is given on anticancer drug development by the group (AWO). 4 Compds. for anticancer treatment are presented which are qualified as candidates for clin. trials. The chemical names, chemical structures, mechanisms of action, and antitumor activity are described of KP 735, **KP 1019**, E 91, and SUM 4.
IT **124875-20-3, KP 1019**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(development of anticancer agents)
RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

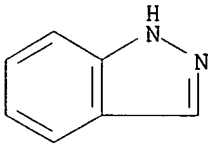
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bauer, R	1995	31A	S28	Eur J Cancer	
Berger, M	1989	9	761	Anticancer Res	HCAPLUS
Brix, H	1990	116	538	J Cancer Res Clin On	MEDLINE
Depenbrock, H	1997	33	2404	Eur J Cancer	HCAPLUS
Fruhauf, S	1991	51	2943	Cancer Res	MEDLINE
Hanauske, A	1997		869	Cancer Medicine. Fou	
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Klenner, T	1990	116	341	J Cancer Res Clin On	MEDLINE
Rank, P	1996	73	315	Ann Hematol	

L77 ANSWER 14 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:155068 HCAPLUS
DN 132:302929
TI A spectroscopic study of the reaction of NAMI, a novel ruthenium(III) anti-neoplastic complex, with bovine serum albumin
AU Messori, Luigi; Orioli, Pierluigi; Vullo, Daniela; Alessio, Enzo; Iengo, Elisabetta
CS Department of Chemistry, University of Florence, 50121, Italy
SO European Journal of Biochemistry (**2000**), 267(4), 1206-1213
CODEN: EJBCAI; ISSN: 0014-2956
PB Blackwell Science Ltd.
DT Journal
LA English
AB The reaction of Na[transRuCl4Me2SO(Im)] (NAMI; where Im is imidazole), a novel antineoplastic ruthenium(III) complex, with BSA, was studied in detail by various physico-chemical techniques. It is shown that NAMI, following chloride hydrolysis, binds bovine serum albumin tightly; spectrophotometric and atomic absorption data point out that up to five ruthenium ions are bound per albumin mol. when BSA is incubated for 24 h with an eightfold excess of NAMI. CD and electronic absorption results show that the various ruthenium centers bound to albumin exhibit well distinct spectroscopic features. The first ruthenium equivalent produces a characteristic pos. CD band at 415 nm whereas the following NAMI equivalent produce less specific and less marked spectral effects. At high NAMI/BSA molar ratios a broad neg. CD band develops at 590 nm. Evidence is provided that the bound ruthenium centers remain in the oxidation state +3. By analogy with the case of transferrins it is proposed that the BSA-bound ruthenium ions are ligated to surface histidines of the protein; results from chemical modification expts. with diethylpyrocarbonate seem to favor this view. Spectral patterns similar to those shown by NAMI are observed when BSA is reacted with two strictly related ruthenium(III) complexes Na[transRuCl4(Me2SO)2] and H(Im)[transRuCl4(Im)2] (ICR), implying a similar mechanism of interaction in all cases. It is suggested that the described NAMI-BSA adducts may form in vivo and may be relevant for the

biol. properties of this complex; alternatively NAMI-BSA adducts may be tested as specific carriers of the ruthenium complex to cancer cells. Implications of these findings for the mechanism of action of NAMI and of related ruthenium(III) complexes are discussed.

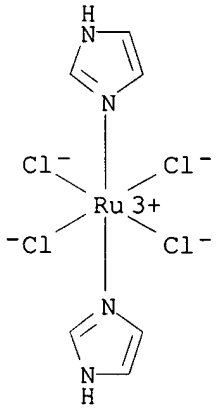
IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(a spectroscopic study of the reaction of NAMI, a novel ruthenium(III) antineoplastic complex, with bovine serum albumin)

RN 103875-27-0 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

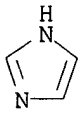
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Alessio, E	1997		457	Cytotoxic, Mutagenic	HCAPLUS
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Christendat, D	1996	35	4468	Biochemistry	HCAPLUS
Clarke, M	1987	33	728	Metal Ions in Biolog	
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1993			Metal Complexes in C	
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Kratz, F	1994	1	169	Metal Based Drugs	HCAPLUS
Kratz, F	1996	3	15	Metal Based Drugs	HCAPLUS
Kratz, F	1992	2	69	Metal Ions in Biolog	
Lundblad, R	1995			Techniques in Protei	
Messori, L	1996	3	1	Metal Based Drugs	HCAPLUS
Mestroni, G	1994	1	41	Chem Behav Pharmaceu	HCAPLUS
Rodger, A	1997			Circular Dichroism a	
Sava, G	1992	3	25	Anti-Cancer Drugs	HCAPLUS
Sava, G	1995	95	109	Chem Biol Interact	HCAPLUS
Sava, G	1992	10	273	Exp Metastasis	HCAPLUS
Sava, G	1996	68	60	Int J Cancer	HCAPLUS
Sava, G	1999	1	143	Topics Bioinorg Chem	HCAPLUS
Smith, C	1996	1	424	J Biol Inorg Chem	HCAPLUS
Sundberg, R	1973	3	39	Bioinorg Chem	HCAPLUS
Winkler, J	1992	92	369	Chem Rev	HCAPLUS

L77 ANSWER 15 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:550474 HCAPLUS
DN 131:280631
TI Synthesis of tumor-inhibiting complex salts containing the anion trans-tetrachlorobis(indazole)ruthenate(III) and crystal structure of the tetraphenylphosphonium salt
AU Peti, Wolfgang; Pieper, Thomas; Sommer, Martina; **Keppler, Bernhard K.**; Giester, Gerald
CS Institute General Inorganic Chemistry, Univ. Vienna, Vienna, A-1090, Austria
SO European Journal of Inorganic Chemistry (**1999**), (9), 1551-1555
CODEN: EJICFO; ISSN: 1434-1948
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
AB Indazolium trans-tetrachlorobis(indazole)ruthenate(1-) exhibits excellent results against different tumor models in vitro and in vivo. To improve the water solubility necessary for the introduction of this tumor-inhibiting compound into clin. trials, the authors synthesized the corresponding Na salt in a 2-step ion exchange via the tetramethylammonium salt. The Na salt shows a 3,5-fold higher solubility in water relative to the indazolium salt. The authors also synthesized the n-butylammonium, n-octylammonium, and tetraphenylphosphonium salts, all of which showed improved solubility in organic solvents. The x-ray crystal structure of the latter could be solved, proving the trans configuration of the complex anion (triclinic, P.hivin.1, a = 11.000(2), b = 13.503(2), c = 14.471(2) Å, α = 65.42(1), β = 82.80(1), γ = 67.93(1)°, V = 1810.2 Å3, Z = 2, ρc = 1.50 g/cm3, μ(MoKα) = 8.1, 5573 observed reflections with Fo > 4σ(Fo), 562 refined parameters, R1 = 0.033, wR2 = 0.088). In spite of the paramagnetic Ru(III) center an assignment of the coordinated indazole protons could be made with the help of a COSY experiment
IT **245488-11-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cation exchange)
RN 245488-11-3 HCAPLUS

CN Methanaminium, N,N,N-trimethyl-, (OC-6-11)-tetrachlorobis(1H-indazole-κN2)ruthenate(1-) (9CI) (CA INDEX NAME)

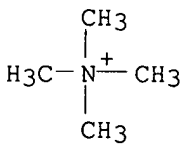
CM 1

CRN 189556-38-5
CMF C14 H12 Cl4 N4 Ru
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 51-92-3
CMF C4 H12 N



IT **197722-94-4P**
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and crystal and mol. structure of)
RN 197722-94-4 HCAPLUS
CN Phosphonium, tetraphenyl-, (OC-6-11)-tetrachlorobis(1H-indazole-κN2)ruthenate(1-) (9CI) (CA INDEX NAME)

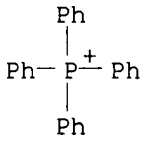
CM 1

CRN 189556-38-5
CMF C14 H12 Cl4 N4 Ru
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 18198-39-5
CMF C24 H20 P



IT **197723-00-5P 245488-07-7P 245488-14-6P 245488-17-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 197723-00-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, sodium, (OC-6-11)-(9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 245488-07-7 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, sodium, trihydrate, (OC-6-11)- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 245488-14-6 HCAPLUS
CN 1-Butanaminium, N,N,N-tributyl-, (OC-6-11)-tetrachlorobis(1H-indazole-κN2)ruthenate(1-) (9CI) (CA INDEX NAME)

CM 1

CRN 189556-38-5
CMF C14 H12 Cl4 N4 Ru
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 10549-76-5
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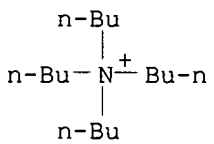


RN 245488-17-9 HCAPLUS
CN 1-Octanaminium, N,N,N-trioctyl-, (OC-6-11)-tetrachlorobis(1H-indazole-κN2)ruthenate(1-) (9CI) (CA INDEX NAME)

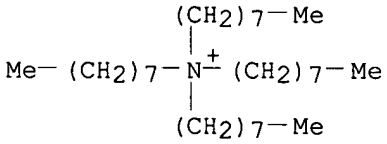
CM 1

CRN 189556-38-5
CMF C14 H12 Cl4 N4 Ru
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 19524-73-3
CMF C32 H68 N



IT **124875-20-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant for preparation of tetraphenylphosphonium trans-

tetrachlorobis(indazole)ruthenate(III))
RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
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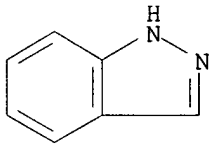


RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1997		457	Cytotoxic, Mutagenic	HCAPLUS
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Clarke, M	1993		129	Metal Complexes in C	HCAPLUS
Depenbrock, H	1997	33	2404	Europ J Cancer	HCAPLUS
Galeano, A	1992	42(I)	821	Arzneimittelforschun	
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Lipponer, K	1996	3	243	Metal-Based Drugs	HCAPLUS
Mestroni, G	1993	1	41	Metal Based Drugs	
Sava, S	1998	16	371	Clin Exp Metastasis	
Seelig, M	1990		476	Metal Ions in Biolog	HCAPLUS
Sheldrick, G	1997			SHELXL-97, A Program	
Sheldrick, G	1997			SHELXS-97, A Program	
van Vliet, P	1995	231	57	Inorg Chim Acta	HCAPLUS
Vilaplana, R	1995	2	211	Metal Based Drugs	HCAPLUS

L77 ANSWER 16 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:490003 HCAPLUS
DN 132:58797
TI Molecular mechanics aided design of antineoplastic agents from ruthenium coordinate complexes
AU Mazumder, U. K.; Gupta, M.; Mukherjee, A.; Mukhopadhyay, D. K.; Dey, P.
CS Departments of Pharmaceutical Technology, Jadavpur University, Calcutta, 700 032, India
SO Indian Journal of Experimental Biology (**1999**), 37(7), 667-670
CODEN: IJEBA6; ISSN: 0019-5189
PB National Institute of Science Communication, CSIR
DT Journal
LA English
AB Through energy minimization using mol. mechanics force field four ruthenium coordinate complexes have been synthesized. Compound I to IV

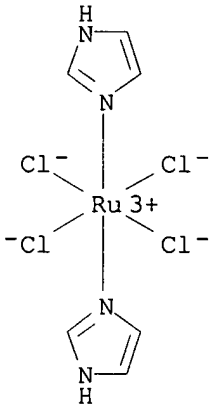
showed antineoplastic activity with varying degree on EAC bearing mice. Mode of action may be through inhibition of antioxidant property of tumor cell as evident from lipid peroxidase activity. Among the complexes Bis pyridine tetrachlororuthenium exhibits highest order of activity with respect to increase mean survival time, inhibition of tumor volume, total blood count, Hb and lipid peroxidase activity.

IT **103875-27-0P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mol. mechanics aided design of antineoplastic agents from ruthenium coordinate complexes)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

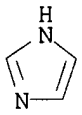
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

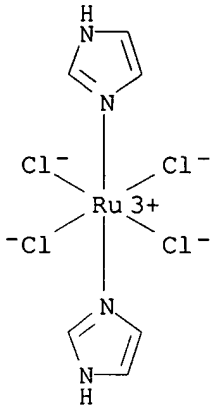
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Barbea, A	1959	10	167	Radiation Res	
Chattopadhyay, S	1989	163	245	Inorg Chim Acta	HCAPLUS
Fruhauf, S	1991	301	27	Cancer Chemother Pha	
Galeano, A	1992	821	42	Arzneimittelforschun	
Keppler, B	1986	166	111	Cancer Res Clic Onco	
Kreuser, E	1992	73	19	Thiel E Semin Oncol	
Lash, E	1966	115	332	Arch, Biochem Biophy	HCAPLUS
Schauenstein, E	1962	64	465	Z Krebsforsch	HCAPLUS
Seelig, M	1992	118	195	Can Res Clin Oncolog	HCAPLUS
Shuster, C	1955	90	423	Proc Soc Exptl Biol	HCAPLUS
Vilaplana, R	1984	575	31	Rev Esp Oncol	
Wick, M	1978	171	163	J Invest Dermatol	
Wilbur, K	1957	13	503	Exptl Cells Res	HCAPLUS

L77 ANSWER 17 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:235969 HCAPLUS
DN 131:67581
TI Investigation of metallodrug-protein interactions by size-exclusion chromatography coupled with inductively coupled plasma mass spectrometry (ICP-MS)
AU Szpunar, Joanna; Makarov, Alexei; Pieper, Thomas; **Keppler, Bernhard K.**; Lobinski, Ryszard
CS Helioparc, EP132, CNRS, Pau, 64000, Fr.
SO Analytica Chimica Acta (**1999**), 387(2), 135-144
CODEN: ACACAM; ISSN: 0003-2670
PB Elsevier Science B.V.
DT Journal
LA English
AB The coupling of size-exclusion HPLC with ICP-MS was developed for the studies of the kinetics of metallodrug binding to human serum proteins. Two platinum- and three ruthenium-based drugs were investigated. Various SEC columns (of different lengths and with different packings) were compared for the separation of the protein-bound and unbound fractions of a metallodrug prior to online detection of the metal (Ru or Pt). The approach developed offers considerable advantages over the methods based on ultrafiltration followed by the off-line metal determination in terms of speed, simplicity, precision and selectivity regarding the mol. weight of the complexes involved.
IT **103875-27-0 124875-20-3 197723-00-5**
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(metallodrug-protein interaction investigation with size-exclusion chromatog. coupled with inductively coupled plasma mass spectrometry)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

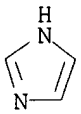
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

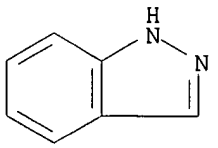
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



RN 197723-00-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, sodium, (OC-6-11)-
(9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baldew, G	1989	491	163	J Chromatogr	HCAPLUS
Bancroft, D	1990	112	6860	J Am Chem Soc	HCAPLUS
Bernareggi, A	1995	669	247	J Chromatogr B	HCAPLUS
Cairns, W	1994	31	295	Anal Proc	HCAPLUS
de Waal, W	1987	407	253	J Chromatogr	HCAPLUS
Einhauser, T	1996	11	747	J Anal At Spectrom	
Elder, R	1990	13	1191	J Liq Chromatogr	HCAPLUS
Elder, R	1993	20	268	J Rheumatol	HCAPLUS
Heim, M	1993		11	Metal Complexes in C	
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1993		11	Metal Complexes in C	
Klenner, T	1993		85	Metal Complexes in C	HCAPLUS
Kratz, F	1994	289	2581	J Biol Chem	
Kratz, F	1993		391	Metal Complexes in C	HCAPLUS
Kratz, F	1992	2	69	Metal Ions in Biolog	
Lipponer, K	1996	3	244	Metal-Based Drugs	
Lobinski, R	1997	51	260A	Appl Spectrosc	HCAPLUS
Lobinski, R	1998	46	271	Talanta	HCAPLUS
Matz, S	1989	4	767	J Anal At Spectrom	HCAPLUS
Mistry, P	1989	24	73	Cancer Chemother Pha	HCAPLUS
Patton, T	1982	10	77	Int J Pharm	HCAPLUS
Reece, D	1987	42	320	Clin Pharmacol Ther	
Reece, P	1984	306	417	J Chromatogr	HCAPLUS
Takahashi, K	1985	76	68	Jpn J Cancer Res	HCAPLUS
Tyczkowska, K	1990	527	447	J Chromatogr	HCAPLUS
Vermorken, J	1982	18	1069	Eur J Cancer Clin On	MEDLINE
Wang, J	1998	120	5793	J Am Chem Soc	HCAPLUS
Zhao, Z	1993	615	83	J Chromatogr	HCAPLUS
Zhao, Z	1993	126	83	J Chromatogr Biomed	
Zhao, Z	1992	10	279	J Pharm Biomed Anal	HCAPLUS
Zoorob, G	1998	128	145	Mikrochim Acta	HCAPLUS
Zunino, F	1989	70	89	Chem Biol Interact	HCAPLUS

L77 ANSWER 18 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:35116 HCAPLUS
DN 130:100672
TI Solvents for therapeutically active metal complexes
IN **Keppler, Bernhard K.**
PA Germany
SO Ger. Offen., 4 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19727978	A1	19990107	DE 1997-19727978	19970701 <--
PRAI DE 1997-19727978		19970701 <--		

OS MARPAT 130:100672
AB 2-Pyrrolidone, γ-butyrolactone, and their derivs. are solvents for therapeutically useful metal complexes, especially poorly soluble Ru and Pt

complexes, and are useful in preparation of pharmaceutical compns. containing these
complexes, especially trans-indazolium tetrachlorobis(indazole)ruthenate(III) (no data).
IT **124875-20-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(solvents for therapeutically active metal complexes)
RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

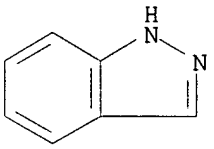
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 19 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:271270 HCAPLUS
DN 129:49288
TI Comparative nephrotoxicity of some antitumor-active platinum and ruthenium complexes in rats
AU Kersten, Lothar; Braunlich, Helmut; **Keppler, Bernhard K.**; Gliesing, Christiane; Wendelin, Matthias; Westphal, Jens
CS Inst. Pharmacology and Toxicology, Friedrich Schiller Univ., Jena, Germany
SO Journal of Applied Toxicology (**1998**), 18(2), 93-101
CODEN: JJATDK; ISSN: 0260-437X
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB The nephrotoxicity of three platinum (CPL, KP734, KP735) and three ruthenium coordination complexes (KP418, KP692, **KP1019**) was tested in rats in comparison to cisplatin (CP). Renal functional changes (excretion of water, protein, p-aminohippurate (PAH) and osmolytes) were not observed after the administration of 10% of the LD50 of the compds. given twice a week for up to 5 wk. After a relatively high single dose of the substances (50% of the LD50), signs of nephrotoxicity on the day of maximal renal damage decreased in the following order: CP, KP418, CPL, KP734, KP735, KP692 and **KP1019**. In comparison to CP, proteinuria was significantly lower after the administration of any of the compds., especially KP692 and **KP1019**. Neither renal lipid peroxidn. (TBARS) nor glutathion status (GSH, GSSG) was affected. In summary, KP735

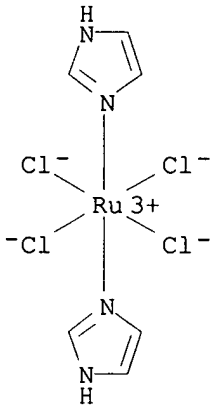
in the group of platinum complexes and **KP1019** in the ruthenium group had the lowest nephrotoxicity. Other investigators have shown that all complexes induced anti-neoplastic activity under analogous exptl. conditions.

IT **103875-27-0 124875-20-3**
RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(nephrotoxicity of antitumor-active platinum and ruthenium complexes in rats)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

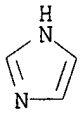
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

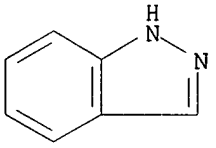
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



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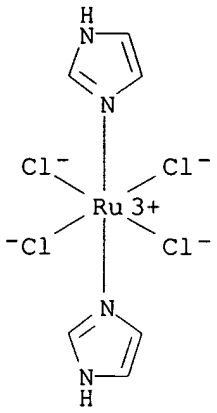
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Appenroth, D	1988	47	791	Biomed Biochim Acta	HCAPLUS
Berger, M	1989	9	761	Anticancer Res	HCAPLUS
Bogin, E	1994	32	843	Eur J Clin Chem Clin	HCAPLUS
Bradford, M	1976	72	248	Anal Biochem	HCAPLUS
Bratton, A	1939	128	537	J Biol Chem	HCAPLUS
Braunlich, H	1983	38	483	Pharmazie	MEDLINE
Ceriotti, G	1989	8	295	Clin Chim Acta	
Cross, R	1950	161	181	Am J Physiol	HCAPLUS
Daugaard, G	1989	25	1	Cancer Chemother Pha	HCAPLUS
Drees, M	1995	31A	356	Eur J Cancer	HCAPLUS
Ellman, G	1979	93	98	Anal Biochem	HCAPLUS
Filastre, J	1989	46	163	Toxicol Lett	
Fisher, R	1994	13	517	Hum Exp Toxicol	HCAPLUS
Fruhauf, S	1991	51	2943	Cancer Res	MEDLINE
Gemba, M	1991		315	Nephrotoxicity, Mech	HCAPLUS
Gliesing, C	1990			Dissertation Medizin	
Hirsch, G	1976	15	89	Environ Health Persp	HCAPLUS
Hissin, P	1976	74	214	Anal Biochem	HCAPLUS
Jones, M	1991	29	29	Cancer Chemother Pha	HCAPLUS
Kameyama, Y	1990	52	15	Toxicol Lett	HCAPLUS
Keppler, B	1990	19	243	Adv Drug Res	HCAPLUS
Kersten, L	1968	10	195	Z Versuchstierk	HCAPLUS
Klenner, T	1988	114	162	J Cancer Res Clin On	
Kluwe, W	1981	57	414	Toxicol Appl Pharmac	HCAPLUS
Kratz, F	1992	2	69	Metal Ions in Biolog	
Kreuser, E	1992	19	73	Sem Oncol	
Leibbrandt, M	1995	132	245	Toxicol Appl Pharmac	HCAPLUS
McGuinness, S	1994	8	1203	Toxicol in Vitro	HCAPLUS
Meyer, K	1994	20	201	Miner Electrolyte Me	HCAPLUS
Nosaka, K	1992	41	73	Kidney Int	HCAPLUS
Pendyala, L	1995	36	271	Cancer Chemother Pha	HCAPLUS
Presnov, M	1988	58	43	Arch Geschwulstforsc	HCAPLUS
Preuss, H	1987	41	1695	Life Sci	HCAPLUS
Sava, G	1991	11	1103	Anticancer Res	HCAPLUS
Sava, G	1995	95	109	Chem-Biol Interact	HCAPLUS
Sava, G	1990		471	Metal Ions in Biolog	HCAPLUS
Sugihara, K	1987	44	71	Jpn J Pharmacol	HCAPLUS

Uozumi, J	1995	195	231	Res Exp Med	HCAPLUS
Vermeulen, N	1992	44	1193	Biochem Pharmacol	HCAPLUS
Weiss, R	1993	46	360	Drugs	HCAPLUS
Wolfgang, G	1994	22	73	Fundam Appl Toxicol	HCAPLUS
Yagi, K	1987	45	337	Chem Phys Lipids	HCAPLUS

L77 ANSWER 20 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:231294 HCAPLUS
DN 128:278755
TI Studies into the mode of action of trans-HInd[RuCl4(ind)2] and trans-HIm[RuCl4(im)2]
AU **Keppler, Bernhard K.**; Pieper, Thomas
CS Inst. fur Anorganische Chemie, Univ. Wien, Vienna, A-1090, Austria
SO Bioinorganic Chemistry (**1997**), 123-128. Editor(s): Trautwein, Alfred X. Publisher: Wiley-VCH Verlag GmbH, Weinheim, Germany. CODEN: 65TRAJ
DT Conference
LA English
AB The tumor-inhibiting ruthenium(III) complexes trans-HIm[RuCl4(i.m.)2] and trans-HInd[RuCl4(ind)2] show promising antitumor activity in different tumor models, especially colon carcinomas. To obtain an insight into the mode of action of these complexes, the aquation chemical as well as the reactions with serum proteins and polynucleotides have been investigated. In comparison, the two complexes show remarkable differences in their stability in physiol. buffer and in their binding rates to apotransferrin. They bind to polynucleotide, showing selectivity in their binding towards poly(dG)·poly(dC) and poly(dA)·poly(dT).
IT **103875-27-0 124875-20-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(studies into the mode of action of antitumor ruthenium complexes)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

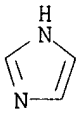
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

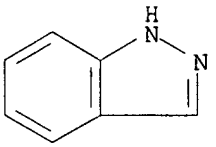
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



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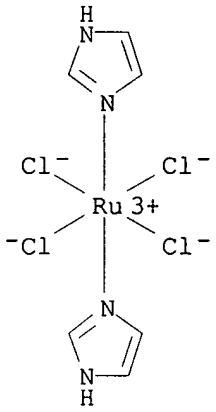
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baker, E	1992	47	147	J Inorg Biochem	HCAPLUS
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Clarke, M	1989	10	25	Progr Clin Biochem M	HCAPLUS
Hartmann, M	1996	15	1741	Chem Commun	
Holler, E	1991	41	1065	Arzneim-Forsch/Drug	
Howe-Grant, M	1980	11	63	Metal Ions Biol Syst	HCAPLUS
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Keppler, B	1990	14	389	New J Chem	HCAPLUS
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Kratz, F	1992	2	69	Metal Ions in Biolog	
Ni Dhubhghaill, O	1994		3305	J Chem Soc Dalton Tr	HCAPLUS
Reedijk, J	1996		801	J Chem Soc, Chem Com	HCAPLUS
Smith, C	1996	1	424	JBIC	HCAPLUS

L77 ANSWER 21 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:70562 HCAPLUS
DN 128:200651
TI Preclinical activity of trans-indazolium [tetrachlorobisindazoleruthenate (III)] (NSC 666158; IndCR; **KP 1019**) against tumor colony-forming units and hematopoietic progenitor cells
AU Depenbrock, H.; Schmelcher, S.; Peter, R.; **Keppler, B. K.**; Weirich, G.; Block, T.; Rastetter, J.; Hanauske, A. -R.
CS Klinikum rechts der Isar, Technische Universitat Munchen, Abteilung Hamatologie und Onkologie, Munchen, D-81675, Germany
SO European Journal of Cancer (**1997**), 33(14), 2404-2410
CODEN: EJCAEL; ISSN: 0959-8049
PB Elsevier Science Ltd.
DT Journal
LA English
AB Trans-indazolium [tetrachlorobisindazoleruthenate(III)] (**KP 1019**) is a new heavy metal complex with promising activity against tumor cell lines and in animal models. We studied the antineoplastic effects of **KP 1019** (final concns.: 1, 10, 100 μg/mL) on in vitro proliferation of clonogenic cells from freshly explanted human tumors in a capillary soft agar cloning system, and compared the activity of **KP 1019** with conventional antineoplastic agents. 53 Of 75 specimens (71%) showed adequate growth in controls. **KP 1019** inhibited tumor colony formation in a concentration-dependent manner in both short- (1 h) and long-term (21 d) exposure expts. **KP 1019** at 100 μg/mL with 1 h exposure was as active as bleomycin, cisplatin, doxorubicin, etoposide, 5-fluorouracil, methotrexate, mitomycin-C and vinblastine, with only paclitaxel more active than **KP 1019** (P=0.002). The antitumor activity of **KP 1019** was more pronounced after long-term exposure, indicating the potential schedule dependency of **KP 1019**. Activity was observed against non-small cell lung, breast and renal cancer. We conclude that if appropriate plasma levels can be achieved in patients, **KP 1019** may have significant clin. activity against a variety of different tumor types.
IT **103875-27-0**
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(trans-indazolium antitumor effect in comparison to conventional

antineoplastic agents and hematotoxicity)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

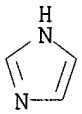
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

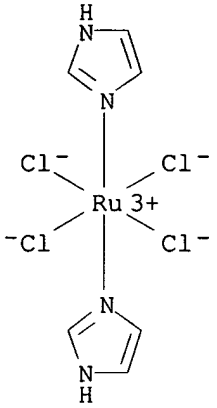
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alberts, D	1980		351	Cloning of Human Tum	HCAPLUS
Berger, M	1989	9	761	Anticancer Res	HCAPLUS
Clarke, M	1989	10	25	Prog Clin Biochem Me	HCAPLUS
Fruhauf, S	1991	27	301	Cancer Chemother Pha	MEDLINE
Fruhauf, S	1991	51	2943	Cancer Res	MEDLINE
Galeano, A	1992	42	821	Arzneimittelforschun	HCAPLUS
Hanauske, A	1985	9	1	Curr Probl Cancer	MEDLINE
Hanauske, U	1987	5	170	Int J Cell Cloning	HCAPLUS
Keppler, B	1990	19	243	Advances Drug Res	HCAPLUS
Keppler, B	1990	17	261	Cancer Treat Rev	HCAPLUS

Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Klausner, R	1983	258	4715	J Biol Chem	HCAPLUS
Kreuser, E	1992	19	73	Semin Oncol	HCAPLUS
Maurer, H	1981	68	381	Naturwiss	MEDLINE
Seelig, M	1992	118	195	J Cancer Res Clin On	HCAPLUS
Von Hoff, D	1986	46	4012	Cancer Res	MEDLINE

L77 ANSWER 22 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:753660 HCAPLUS
DN 128:69919
TI Imidazole release from the antitumor-active ruthenium complex imidazolium trans-tetrachlorobis(imidazole)ruthenate(III) by biologically occurring nucleophiles
AU Hartmann, Markus; Lipponer, Karl-Georg; **Keppler, Bernhard K.**
CS Institut fur Anorganische Chemie, Universitat Wien, Wahringer Strasse 42, Vienna, A-1090, Austria
SO Inorganica Chimica Acta (**1998**), 267(1), 137-141
CODEN: ICHAA3; ISSN: 0020-1693
PB Elsevier Science S.A.
DT Journal
LA English
AB The antitumor-active complex HIm[trans-RuIIICl4(Im)2], imidazolium trans-tetrachlorobis(imidazole)ruthenate(III), completely changes its ligand configuration within 1 h in H2O in the presence of L-histidine and L-glutathione. The observed release of the trans-standing imidazole ligands at 37° that occurs in addition to chloride substitution reactions has to be taken into consideration for further studies into the mode of action of this new antitumor drug.
IT **103875-27-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(substitution of imidazole with histidine)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

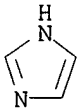
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anderson, C	1995	73	471	Can J Chem	HCAPLUS
Anderson, C	1995	34	6065	Inorg Chem	HCAPLUS
Anderson, C	1995	233	33	Inorg Chim Acta	HCAPLUS
Berners-Price, S	1990	38	305	J Inorg Biochem	HCAPLUS
Bertini, I	1986		1	NMR of Paramagnetic	
Bloemink, M	1996	32	641	Metal Ions in Biolog	HCAPLUS
Brown, G	1978	100	2767	J Am Chem Soc	HCAPLUS
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Clarke, M	1989	10	25	Prog Clin Biochem Me	HCAPLUS
Comess, K	1993	1	134	Molecular Aspects of	
Frankfurt, O	1991	51	1190	Cancer Res	HCAPLUS
Freeman, H	1967	22	257	Adv Protein Chem	MEDLINE
Hartmann, M	1996		1741	J Chem Soc, Chem Com	HCAPLUS
Isied, S	1976	15	3070	Inorg Chem	HCAPLUS
Kane, S	1996	35	2180	Biochemistry	HCAPLUS
Keppler, B	1989	10	41	Prog Clin Biochem Me	HCAPLUS
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Kratz, F	1992	2	69	Metal Ions in Biolog	
Kratz, F	1994	1	169	Metal-based Drugs	HCAPLUS
Lippert, B	1981	56	L23	Inorg Chim Acta	HCAPLUS
Ni Dhubhghaill, O	1994		3305	J Chem Soc, Dalton T	HCAPLUS

Payet, D	1995	2	137	Metal-based Drugs	HCAPLUS
Reedijk, J	1996		801	J Chem Soc, Chem Com	HCAPLUS
Rupp, W	1987	26	4366	Inorg Chem	
Smith, C	1996	1	424	J Biol Inorg Chem	HCAPLUS
Sundberg, R	1972	94	6558	J Am Chem Soc	HCAPLUS
Sundberg, R	1974	96	381	J Am Chem Soc	HCAPLUS
Tobe, M	1987	1	300	Comprehensive Coordi	
Tsutsui, M	1971	1	115	J Coord Chem	HCAPLUS
Whelan, R	1989	1	359	Cancer Commun	HCAPLUS
Wilkins, R	1991		199	Kinetics and Mechani	

L77 ANSWER 23 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:675538 HCAPLUS
DN 127:325682
TI Preparation of ruthenium(III) complexes with tumor inhibiting properties
IN **Keppler, Bernhard K.**
PA Keppler, Bernhard K., Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19612291	A1	19971002	DE 1996-19612291	19960328 <--
	WO 9736595	A2	19971009	WO 1997-EP1643	19970401 <--
	WO 9736595	A3	19971106		
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 835112	A2	19980415	EP 1997-918095	19970401 <--
	EP 835112	B1	20030910		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	AT 249221	E	20030915	AT 1997-918095	19970401 <--
	PT 835112	T	20040130	PT 1997-918095	19970401 <--
	ES 2205205	T3	20040501	ES 1997-918095	19970401 <--
PRAI	DE 1996-19612291	A	19960328	<--	
	WO 1997-EP1643	W	19970401	<--	

OS MARPAT 127:325682
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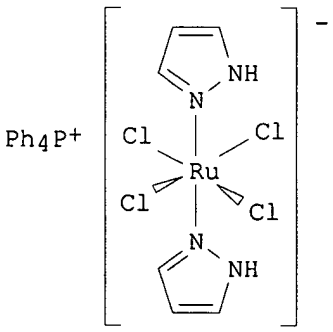


I

AB The preparation of title complexes, {G}-(n+p+2r(p-1)-3){[RuX6-n-p-q-2rBn(H2O)p(OH)q(O)r]2r+1}n+p+2r(p-1)-3 [n + p + 2r(p - 1) - 3q ≠ 0; G = counterion; B = multiple nitrogen containing heterocycle; X = halo, pseudohalo, HCO3-, RCO2-, R = alkyl, alkenyl, (un)substituted C1-6 aryl; n = 1-3; p, q = 0.5, 0, 1; r = 0, 0.5], useful as cancer treating agents (no data), is described. Thus, reaction of trans-imidazolium tetrachlorobis(imidazole)ruthenate(III) with Ph4PI in methanol gave title complex I in 90% yield.

IT **124875-20-3 197723-03-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of ruthenium complexes with tumor inhibiting properties)

RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

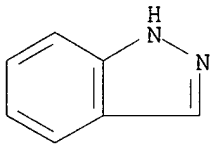
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

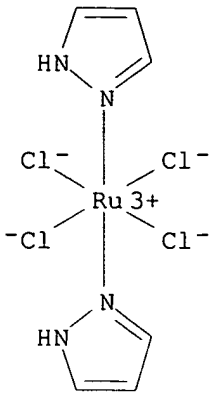
CRN 271-44-3
CMF C7 H6 N2



RN 197723-03-8 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-pyrazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

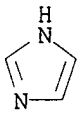
CRN 124951-56-0
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

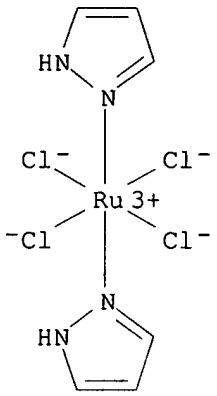
CRN 288-32-4
CMF C3 H4 N2



IT **197722-91-1P 197722-94-4P 197722-97-7P**
197723-00-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of ruthenium complexes with tumor inhibiting properties)
RN 197722-91-1 HCAPLUS
CN Phosphonium, tetraphenyl-, (OC-6-11)-tetrachlorobis(1H-pyrazole-κN2)ruthenate(1-) (9CI) (CA INDEX NAME)

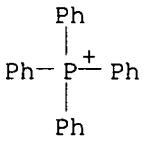
CM 1

CRN 197722-90-0
CMF C6 H8 Cl4 N4 Ru
CCI CCS



CM 2

CRN 18198-39-5
CMF C24 H20 P



RN 197722-94-4 HCAPLUS
CN Phosphonium, tetraphenyl-, (OC-6-11)-tetrachlorobis(1H-indazole-κN2)ruthenate(1-) (9CI) (CA INDEX NAME)

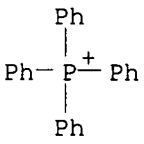
CM 1

CRN 189556-38-5
CMF C14 H12 Cl4 N4 Ru
CCI CCS

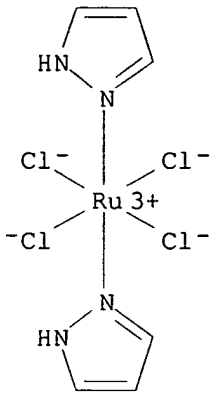
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 18198-39-5
CMF C24 H20 P



RN 197722-97-7 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-pyrazole-κN2)-, sodium, (OC-6-11)-(9CI) (CA INDEX NAME)



● Na^+

RN 197723-00-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, sodium, (OC-6-11)-(9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 24 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:323731 HCAPLUS
DN 127:30626
TI Structural and functional flexibility of lactoferrin
AU Baker, Edward N.; Anderson, Bryan F.; Baker, Heather M.; Faber, H. Rick; Smith, Clyde A.; Sutherland-Smith, Andrew J.
CS Department of Chemistry and Biochemistry, Massey University, Palmerston North, N. Z.
SO Experimental Biology and Medicine (Totowa, New Jersey) (**1997**), 28(Lactoferrin), 177-191
CODEN: EBIMFW
PB Humana
DT Journal
LA English
AB Lactoferrin is a protein that binds iron with great affinity, yet is also able to release it. It also binds a variety of other metal ions and anions. To investigate its mechanisms of binding and release, and the reasons for its versatility in binding, we have undertaken x-ray crystallog. studies on various forms of lactoferrin. The structure of a new crystal form of apolactoferrin, at 3.5-Å resolution, has shown that in each lobe the binding cleft is in an open state, but that the size of the conformational change, compared with diferric lactoferrin, varies: a domain rotation of 54° in the N-lobe and 18° in the C-lobe. Comparison with the previously determined apolactoferrin structure, in which the C-lobe is closed, leads to a dynamic model for iron binding. The crystal structure of oxalate-substituted diferric lactoferrin shows that larger anions can be accommodated without affecting domain closure, although the two binding sites adjust differently. Solution studies also indicate that larger cations, such as Ce4+, may also be able to bind within the same closed structure. In this case, Ce3+ is oxidized to Ce4+ when it binds to lactoferrin, with a visible spectrum similar to those of Fe3+, Mn3+, and Co3+. Crystallog. binding studies using ruthenium

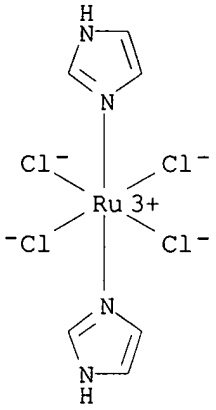
complexes with antitumor activity show that these bind with high affinity in the binding cleft of apolactoferrin and more weakly in nonspecific external sites. This suggests possible uses of lactoferrin in drug delivery.

IT **103875-27-0 124875-20-3 186179-42-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(structural and functional flexibility of lactoferrin)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

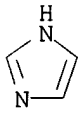
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

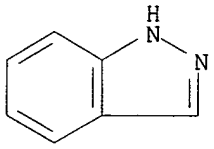
CRN 124875-19-0

CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

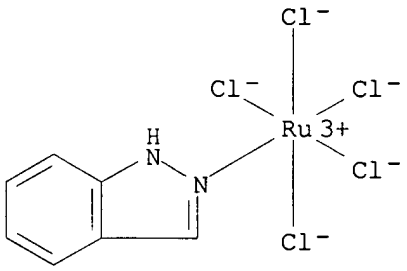
CRN 271-44-3
CMF C7 H6 N2



RN 186179-42-0 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-indazole-κN2)-, (OC-6-21)-, dihydrogen, compd. with 1H-indazole (1:2) (9CI) (CA INDEX NAME)

CM 1

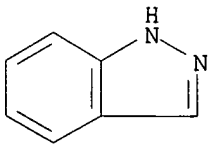
CRN 186179-41-9
CMF C7 H6 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



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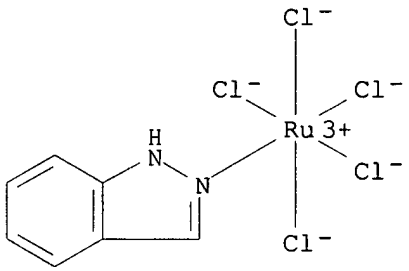
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ainscough, E	1979	33	149	Inorg Chim Acta	HCAPLUS
Anderson, B	1989	209	711	J Mol Biol	HCAPLUS
Anderson, B	1990	344	784	Nature (Lond)	HCAPLUS
Baker, E	1994	41	389	Adv Inorg Chem	HCAPLUS
Brock, J	1985		183	Metalloproteins, par	HCAPLUS
Grossmann, J	1992	225	811	J Mol Biol	HCAPLUS
Harris, D	1989		241	Iron Carriers and Ir	
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Mazurier, J	1980	629	399	Biochim Biophys Acta	HCAPLUS
Norris, G	1989	209	329	J Mol Biol	HCAPLUS
Oh, B	1993	268	11348	J Biol Chem	HCAPLUS
Pecoraro, V	1981	20	7033	Biochemistry	HCAPLUS
Quiocho, F	1990	326	341	Phil Trans Roy Soc S	HCAPLUS
Sakabe, N	1991	A303	448	Nucl Instrum Meth Ph	HCAPLUS
Smith, C	1994	116	7889	J Am Chem Soc	HCAPLUS

L77 ANSWER 25 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:255715 HCAPLUS
DN 126:325098
TI Binding of ruthenium(III) anti-tumor drugs to human lactoferrin probed by high resolution X-ray crystallographic structure analyses
AU Smith, Clyde A.; Sutherland-Smith, Andrew J.; **Keppler, Bernhard K.**; Kratz, Felix; Baker, Edward N.
CS Department of Biochemistry, Massey University, Palmerston North, N. Z.
SO JBIC, Journal of Biological Inorganic Chemistry (**1996**), 1(5), 424-431
CODEN: JJBCFA; ISSN: 0949-8257
PB Springer
DT Journal
LA English
AB The binding to human lactoferrin of three Ru(III) complexes with anti-tumor activity has been investigated by x-ray crystallog. to gain insights into how such complexes might be carried during transferrin-mediated delivery to cells. The complexes, HIm[RuIm2Cl4], HInd[RuInd2Cl4] and (HInd)2[RuIndCl5], where Im = imidazole and Ind = indazole, were diffused into crystals of apo-lactoferrin (apoLf). X-ray diffraction data were collected to 2.6 Å, 2.2 Å and 2.4 Å resp. The binding sites for the Ru complexes were determined from difference Fouriers, in comparison with native apoLf; the two indazole-apoLf complexes were also refined crystallog. to final R factors of 0.202 (for 8.0 to 2.3 Å data) and 0.192 (for 8.0 to 2.4 Å data), resp. Two types of binding site were identified, a high-affinity site at His 253 in the open N-lobe iron-binding cleft of apoLf (and by analogy a similar one at His 597 in the C-lobe), and lower-affinity sites at surface-exposed His residues, primarily His 590 and His 654. The exogenous heterocyclic ligands remain bound to Ru, at least at the His 253 site, and modeling suggests that the nature and number of these ligands may determine whether the closed structure that is required for receptor binding could be formed or not. The results also highlight the importance of His residues for binding such complexes and the value of heavy atom binding studies from crystallog. analyses for identifying non-specific binding sites on proteins.
IT **189556-38-5 189556-39-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)

(binding of ruthenium(III) anti-tumor drugs to human lactoferrin probed by high resolution x-ray crystallog. structure analyses)
RN 189556-38-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 189556-39-6 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-indazole-κN2)-, (OC-6-21)- (9CI) (CA INDEX NAME)



L77 ANSWER 26 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:20150 HCAPLUS
DN 126:112830
TI Effects of hypoxia and transferrin on toxicity and DNA binding of ruthenium antitumor agents in HeLa cells
AU Frasca, D.; Ciampa, J.; Emerson, J.; Umans, R. S.; Clarke, M. J.
CS Merkert Chemistry Center, Boston College, Chestnut Hill, MA, 02167, USA
SO Metal-Based Drugs (**1996**), 3(4), 197-209
CODEN: MBADEI; ISSN: 0793-0291
PB Freund
DT Journal
LA English
AB Nuclear DNA binding and inhibition of growth of HeLa cells in culture were determined after 24 h incubation with the ruthenium anticancer agents cis-[Cl2(NH3)4Ru]Cl (CCR) and (ImH)trans-[(Im)2Cl4Ru] (ICR) as a function of [Ru], Po2, and added transferrin. Consistent with the "activation-by-reduction" hypothesis, cytotoxicity and DNA binding for both complexes increased under reduced oxygen conditions. Consistent with the "transferrin-transport" hypothesis, inhibition of cell growth also increased with added transferrin for both complexes. Despite their differences in charge, reduction potentials and substitution rates, both complexes behaved remarkably similarly indicating a common mechanism of action for both. Under atmospheric conditions (Po2 = 159 torr), CCR inhibited HeLa cell growth with IC50 = 3.5 μM, while that for ICR was 2.0 μM. The binding of both complexes to DNA (RuDNA/PDNA) correlated with toxicity and was approx. linear in the concentration of the ruthenium complex in the culture medium, [Ru]. For both complexes, IC50 values decrease and DNA binding increases with decreasing log(Po2). In general, DNA binding at all oxygen pressures for both complexes is in the range of one Ru per 1000-2000 DNA base pairs at [Ru] = IC50.
IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)

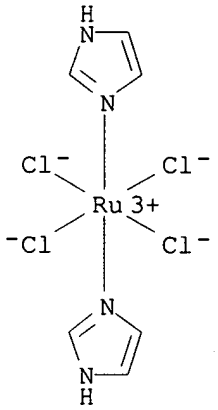
(effects of hypoxia and transferrin on toxicity and DNA binding of ruthenium antitumor agents in HeLa cells)

RN 103875-27-0 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

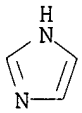
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Berger, M	1989	9	761	Anticancer Res	HCAPLUS
Broomhead, A	1968	7	2519	Inorg Chem	
Clarke, M	1996		35	Inorg Chem, in press	
Clarke, M	1974	96	5413	J Am Chem Soc	HCAPLUS
Clarke, M	1978	100	5068	J Am Chem Soc	HCAPLUS
Clarke, M	1980	11	231	Met Ions Biol Syst	HCAPLUS
Clarke, M	1996	32	727	Met Ions in Biol Sys	HCAPLUS
Dhubhghaill, O	1994		3305	J Chem Soc Dalt Tran	

Durig, J	1976	13	287	Chem-Biol Interact	HCAPLUS
Johnson, A	1993	210	151	Inorg Chim Acta	HCAPLUS
Kelman, A	1977	7	274	J Clin Hematol Oncol	HCAPLUS
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1987	26	844	Inorg Chem	HCAPLUS
Keppler, B	1989	14	41	Ruthenium and Other	
Kratz, F	1994	269	2581	J Biol Chem	HCAPLUS
Kratz, F	1994	1	169	Metal-Based Drugs	HCAPLUS
Lippard, S	1994			Principles of Bioino	
Marx, K	1989	90	37	Mol Cell Biochem	HCAPLUS
Marx, K	1989	86	155	Molec Cell Biochem	HCAPLUS
Messori, L	1996	3	1	Metal-Based Drugs	HCAPLUS
Miklavcic, D	1990	9	133	J Bioelect	
Okunieff, P	1994	345	485	Adv Exp Med Biol	MEDLINE
Seelig, M	1992	118	195	J Cancer Res Clin On	HCAPLUS
Shepherd, R	1992	31	1457	Inorg Chem	HCAPLUS
Som, P	1983	8	491	Eur J Nucl Med	HCAPLUS
Srivastava, S	1979	265-2		Radiopharmaceuticals	
Srivastava, S	1989	10	111	Ruthenium and other	HCAPLUS
Vaupel, P	1991	51	3316	Canc Res	MEDLINE
Yasbin, R	1980	30	355	Chemico-Biol Interac	

L77 ANSWER 27 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:7889 HCAPLUS
DN 126:126064
TI Synthesis, characterization and solution chemistry of indazolium trans-tetrachlorobis(indazole)ruthenate(III), a new anticancer ruthenium complex. IR, UV, NMR, HPLC, investigations and antitumor activity. Crystal structures of 1-methylindazolium trans-tetrachlorobis-(1-methylindazole)ruthenate(III) and its hydrolysis product trans-monoaquatrichlorobis(1-methylindazole)ruthenate(III)
AU Lipponer, Karl-Georg; Vogel, Ellen; **Keppler, Bernhard K.**
CS Inst. Inorganic Chem., Univ. Heidelberg, Heidelberg, D-69120, Germany
SO Metal-Based Drugs (**1996**), 3(5), 243-260
CODEN: MBADEI; ISSN: 0793-0291
PB Freund
DT Journal
LA English
AB Besides intensive studies into the synthesis of trans-HInd[RuCl4(Ind)2] (Ind = indazole) 1, which differs remarkably from the usual method for the complexes of the HL[RuCl4L2] - type, competitive products and hydrolysis of this species are described. Stability and pseudo-first-order rate constant under physiol. conditions in comparison with the analogous trans-HIm[RuCl4(Im)]2 (Im = imidazole) (I) were examined by HPLC, UV and conductivity measurements (kobs.(1) = 1.55 + 10-4 s-1; kobs. (I) = 9.10 + 10=4 s-1). An attempt was made to elucidate the bonding conditions in 1 by studying the reactions of Ru(III) and the two N-Me isomers of indazole. It can be expected that bonding in the unsubstituted ligand should occur via the N2 N. The mol. structures of H(1-MeInd)[trans-RuCl4(1-MeInd)2].H2O (1-MeInd = 1-methylindazole) 6 and its hydrolysis product in aqueous solution [RuCl3(H2O)(1-MeInd)2] (7) were determined crystallog. After anisotropic refinement of F values by least squares, R is 0.053 for 6 and 0.0.59 for 7. Both complexes crystallize with Z = 4 and monoclinic symmetry. The space group is P2.1/n for 6 with a 10.511 b 13.87, c 19.93 Å and β 98.17° and C2/c for 7 with a 19.90, b 10.94, c 8.490 Å and β 96.74°. The fact that the aqua species 7 could be isolated after dissolving 6 in a H2O/acetone solution confirmed the theory of many Ru(III) complexes being initially transformed, under physiol. conditions, into aqua complexes in a 1st and

often rate-determining hydrolysis step. 1 And I are potent antitumor agents which exhibit activity against a variety of tumor cells and exptl. tumor models in animals, including autochthonous colorectal tumors. Clin. studies with 1 are in preparation

IT **186179-46-4P 186179-47-5P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and crystal structure of)

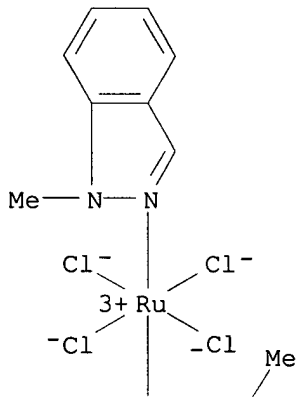
RN 186179-46-4 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1-methyl-1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1-methyl-1H-indazole (1:1), monohydrate (9CI) (CA INDEX NAME)

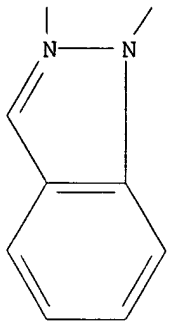
CM 1

CRN 186179-45-3
CMF C16 H16 Cl4 N4 Ru . H
CCI CCS

PAGE 1-A



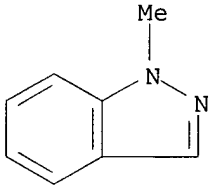
PAGE 2-A



● H^+

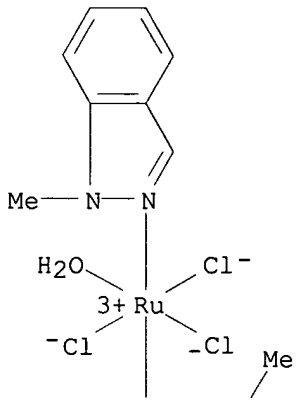
CM 2

CRN 13436-48-1
CMF C8 H8 N2

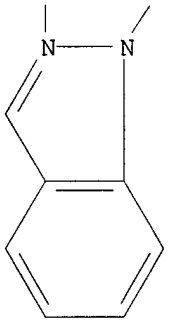


RN 186179-47-5 HCAPLUS
CN Ruthenium, aquatrichlorobis(1-methyl-1H-indazole-κN2)-, (OC-6-21)-(9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



IT **124875-20-3P**
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and kinetics of hydrolysis)
RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

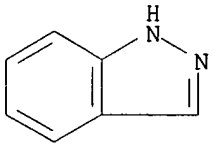
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

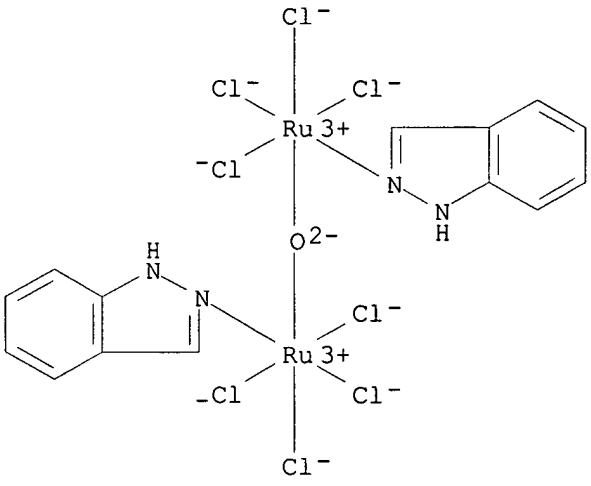
CRN 271-44-3
CMF C7 H6 N2



IT **186179-40-8P 186179-42-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 186179-40-8 HCAPLUS
CN Ruthenate(4-), octachlorobis(1H-indazole-κN2)-μ-oxodi-, tetrahydrogen, compd. with 1H-indazole (1:4) (9CI) (CA INDEX NAME)

CM 1

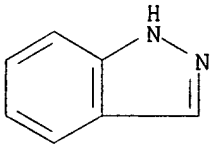
CRN 186179-39-5
CMF C14 H12 Cl8 N4 O Ru2 . 4 H
CCI CCS



● 4 H^+

CM 2

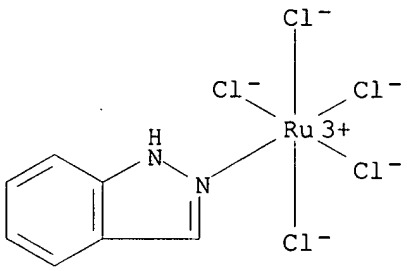
CRN 271-44-3
CMF C7 H6 N2



RN 186179-42-0 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-indazole-κN2)-, (OC-6-21)-, dihydrogen, compd. with 1H-indazole (1:2) (9CI) (CA INDEX NAME)

CM 1

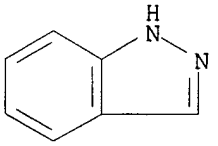
CRN 186179-41-9
CMF C7 H6 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



RETABLE

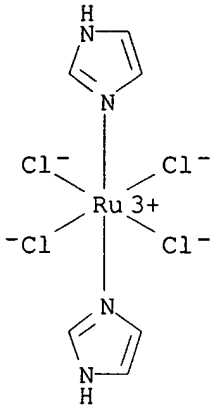
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Alessio, E	1993	203	205	Inorg Chim Acta	HCAPLUS
Anon	1984			DIF4, version 6.1	
Anon	1974	IV		International Tables	
Bakke, J	1975	B29	1089	Acta Chemica Scandin	HCAPLUS
Chatlas, J	1995	233	59	Inorg Chim Acta	HCAPLUS
Clarke, M	1993		129	Metal Complexes in C	HCAPLUS
Garzon, F	1987	19	347	Cancer Chemother Pha	HCAPLUS

Henn, M	1989			Dissertation, Anorg-	
Holler, E	1991	41	10	Arzneim-Forsch/Drug	
Keppler, B	1987	37	770	Arzneim-Forsch/Drug	HCAPLUS
Keppler, B	1987	26	4366	Inorg Chem	HCAPLUS
Keppler, B	1987	26	844	Inorg Chem	HCAPLUS
Keppler, B	1986	111	166	J Cancer Res Clin On	HCAPLUS
Keppler, B	1993		187	Metal Complexes in C	HCAPLUS
Keppler, B	1989	10	41	Progr Clin Biochem M	HCAPLUS
Kratz, F	1994	1	169	Metal-Based Drugs	HCAPLUS
Kratz, F	1996	3	15	Metal-Based Drugs	HCAPLUS
Mestroni, G	1993		157	Metal Complexes in C	HCAPLUS
Mestroni, G	1994	1	43	Metal-Based Drugs	
Ni Dhubhghaill, O	1994		3305	J Chem Soc Dalton Tr	HCAPLUS
Sheldrick, G	1988			SHELXTL-PLUS, Univer	
Vilaplana, R	1995	2	211	Metal-Based Drugs	HCAPLUS

L77 ANSWER 28 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:486670 HCAPLUS
DN 125:185068
TI Two antitumor ruthenium(III) complexes showing selectivity in their binding towards poly(dG)·poly(dC) and poly(dA)·poly(dT)
AU Hartmann, Markus; Einhaeuser, Thorsten J.; **Keppler, Bernhard K.**
CS Anorganisch-Chemisches Institut, Universitaet Heidelberg, Heidelberg, D-69120, Germany
SO Chemical Communications (Cambridge) (**1996**), (15), 1741-1742
CODEN: CHCOFS; ISSN: 1359-7345
PB Royal Society of Chemistry
DT Journal
LA English
AB The antitumor-active complexes trans-[RuIIICl4(Im)2] (Im = imidazole) and trans-[RuIIICl4(ind)2] (ind = indazole) bind at a higher binding rate to poly(dG)·poly(dC), compared to poly(dA)·poly(dT); the covalent binding to the nucleobases requires a preceding aquation of the compds., similar to cisplatin.
IT **103875-27-0 124875-20-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antitumor ruthenium(III) complexes showing selectivity in their binding towards poly(dG)·poly(dC) and poly(dA)·poly(dT))
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

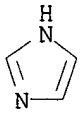
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

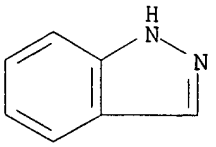
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

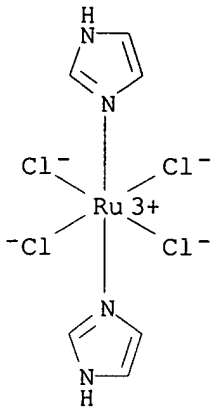
CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 29 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:409048 HCAPLUS
DN 125:131840
TI Comparison of the antiproliferative activity of two antitumor ruthenium(III) complexes with their apotransferrin and transferrin-bound forms in a human colon cancer cell line
AU Kratz, F.; **Keppler, B. K.**; Hartmann, M.; Messon, L.; Berger, M. R.
CS Tumour Biol. Cent., Clinical Res., Freiburg, D-79106, Germany
SO Metal-Based Drugs (**1996**), 3(1), 15-23
CODEN: MBADEI; ISSN: 0793-0291
PB Freund
DT Journal
LA English
AB Two ruthenium(III) complexes, namely trans-indazolium[tetrachlorobis(indazole)-ruthenate(III)], HInd[RuInd2Cl4], and trans-imidazolium[tetrachlorobis(imidazole)-ruthenate(III)], HIm[RuIm2Cl4], exhibit high anticancer activity in an autochthonous colorectal carcinoma model in rats. Recently, it has been shown that both complexes bind specifically to human serum apotransferrin and the resulting adducts have been studied through spectroscopic and chromatog. techniques with the ultimate goal of preparing adducts with good selectivity for cancer cells due to the fact that tumor cells express high amts. of transferrin receptors on their cell surface. To investigate whether the cellular uptake of the complexes was mediated by apotransferrin or transferrin, we compared the antiproliferative efficacy of HInd[RuInd2Cl4] and HIm[RuIm2Cl4] with its apotransferrin- and transferrin-bound form in the human colon cancer cell line SW707 using the microculture tetrazolium test (MTT). Our results show that especially the transferrin-bound forms exhibit high antiproliferative activity, which exceeds that of the free complex, indicating that this protein can act as a carrier of the ruthenium complexes into the tumor cell.
IT **103875-27-0 142388-45-2**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(comparison of the antiproliferative activity of two antitumor ruthenium(III) complexes with their apotransferrin and transferrin-bound forms in a human colon cancer cell line)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

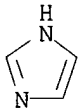
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

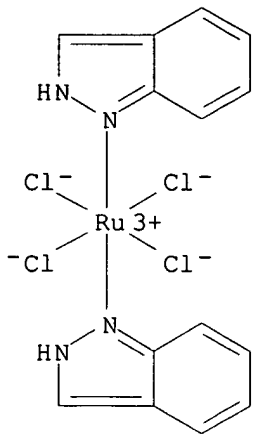
CRN 288-32-4
CMF C3 H4 N2



RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

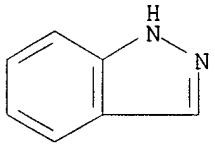
CRN 142388-44-1
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 30 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:903102 HCAPLUS
DN 123:357587
TI Reactions of the Tetrachlorobis(imidazole)ruthenium(III) and Pentachloro(imidazole)ruthenium(III) Anions with Imidazole and N6,N6-Dimethyladenine
AU Anderson, Craig; Beauchamp, Andre L.
CS Departement de Chimie, Universite de Montreal, Montreal, QC, H3C 3J7, Can.
SO Inorganic Chemistry (**1995**), 34(24), 6065-73
CODEN: INOCAJ; ISSN: 0020-1669
PB American Chemical Society
DT Journal
LA English
AB The reactions of (ImH)2[RuCl5Im] (Im = imidazole) in H2O were monitored by 1H NMR spectroscopy. Fast initial aquation of [RuCl5Im]2- to [RuCl4(H2O)Im]- is followed by successive substitutions along two pathways: slow displacement of extra Cl- ligands by H2O to form higher aquation products and attack of an Im ligand to give [RuCl4Im2]-, which then aquates. In the presence of 2 equiv of added Im, (ImH)[RuCl4Im2] gives mixts. of complexes containing three to four Im per Ru, whereas 20 equiv lead to species with five to six Im per Ru. Imidazole-rich species coexist in solution with the starting [RuCl4Im2]- ion. X-ray diffraction

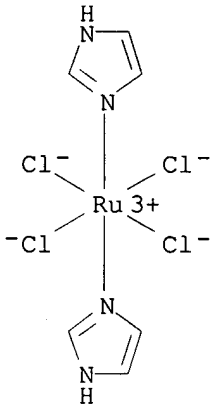
work on [Ru(OH)2Im4][RuCl4Im2] (monoclinic, P21/c, a 13.126, b 10.8833, c 10.6110 Å, β 108.28°, R = 0.045) shows octahedral trans-[Ru(OH)2Im4]+ and trans-[RuCl4Im2]- connected by H bonding. Many complexes and aquation products successively appear when Im is reacted with (ImH)2[RuCl5Im], and species with five to six Im ligands per Ru are again obtained with 20 equiv of added Im. An end product is isolated as yellow crystals and shown by x-ray diffraction (hexagonal, P63/m, a 8.9756, c 20.880 Å, R = 0.023) to be the [RuIm6]CO3·5H2O compound, containing the reduced Ru(II) octahedral [RuIm6]2+. In the presence of N6,N6-dimethyladenine (DMAD), [RuCl4Im2]- in H2O slowly forms the [RuCl3Im2(DMAD)] complex, in which the adenine ligand is monodentate.

IT **103875-27-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(aquation and coordinative substitution of ruthenium chloro imidazole antitumor agents by imidazole or dimethyladenine)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

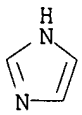
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

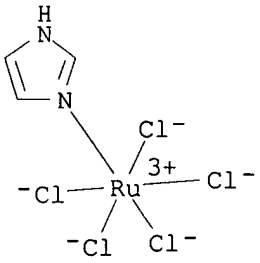
CRN 288-32-4
CMF C3 H4 N2



IT **105085-56-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(aquation and coordinative substitution of ruthenium chloro imidazole antitumor agents by imidazole or dimethyladenine)
RN 105085-56-1 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-imidazole-N3)-, (OC-6-21)-, dihydrogen, compd. with 1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

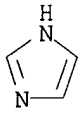
CRN 105085-55-0
CMF C3 H4 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



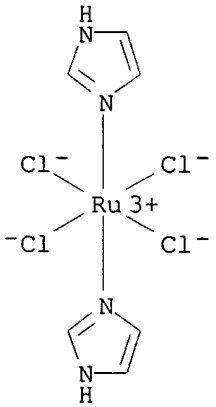
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)
(formation and NMR of

L77 ANSWER 31 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:655606 HCAPLUS
DN 123:153736
TI Spontaneous aquation reactions of a promising tumor inhibitor trans-imidazolium-tetrachlorobis(imidazole)ruthenium(III), trans-HIm[RuCl4(Im)2]
AU Chatlas, J.; van Eldik, R.; **Keppler, B. K.**
CS Institut fuer Anorganische Chemie, Universitaet Erlangen-Nuernberg, Egerlandstrasse 1, Erlangen, 91058, Germany
SO Inorganica Chimica Acta (**1995**), 233(1-2), 59-63
CODEN: ICHAA3; ISSN: 0020-1693

PB Elsevier Sequoia
DT Journal
LA English
AB The spontaneous aquation reaction of trans-RuCl4(Im)2-, Im = imidazole, was studied as a function of pH, chloride concentration, imidazole buffer and temperature, using spectrophotometric and chromatog. techniques. The selected pH and chloride concentration control the degree of aquation observed In all cases evidence for the formation of RuCl3(Im)2H2O was found, which can undergo deprotonation and/or subsequent aquation depending on the pH and free chloride concentration in solution No evidence for aquation of the imidazole ligand was found. The formation of RuCl3(Im)2H2O is characterized by a rate constant of 1.5+10-5 s-1 at 25 °C, ΔH# = 117±7 kJ mol-1 and ΔS# = +55±23 J K-1 mol-1. The results are discussed in reference to the tumor inhibiting properties of the complex.
IT **103875-27-0**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(spontaneous aquation reactions of promising tumor inhibitor trans-imidazolium-tetrachlorobis(imidazole)ruthenium(III), trans-HIm[RuCl4(Im)2])
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

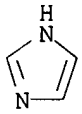
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

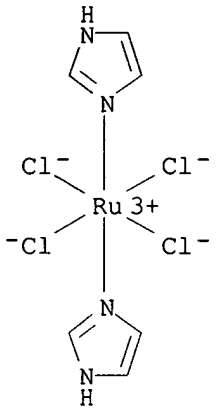
CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 32 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:119151 HCAPLUS
DN 122:436
TI Protein-binding properties of two antitumor Ru(III) complexes to human apotransferrin and apolactoferrin
AU Kratz, F.; **Keppler, B. K.**; Messori, L.; Smith, C.; Baker, E. N.
CS Dep. Inorg. Chem., Univ. Heidelberg, Heidelberg, W-6900, Germany
SO Metal-Based Drugs (**1994**), 1(2-3), 169-73
CODEN: MBADEI; ISSN: 0793-0291
DT Journal
LA English
AB The interaction of two ruthenium(III) complexes exhibiting high anticancer activity, trans-indazolium (bis-indazole) tetrachlororuthenate(III) (HInd[RuInd2Cl4]) and trans-imidazolium (bis-imidazole) tetrachlororuthenate(III) (HIm[RuIm2Cl4]) with human serum apotransferrin has been investigated through spectroscopic and chromatog. techniques with the ultimate goal of preparing adducts with good selectivity for cancer cells due to the fact that tumor cells express high amts. of transferrin receptors on their cell surface. Whereas the binding of HIm[RuIm2Cl4] to human serum apotransferrin takes several hours, HInd[RuInd2Cl4], the less toxic complex, gives rise to a well defined 2:1 complex within a few minutes. HInd[RuInd2Cl4] will react with apotransferrin only in the presence of bicarbonate, this anion dictating the kinetic and mechanistic characteristics of protein-binding. CD studies had previously indicated that binding of both Ru(III) complexes occurs around the unoccupied iron(III) binding sites; this result is now confirmed by preliminary x-ray data of HInd[RuInd2Cl4] and Hlm[RuIm2Cl4] bound to apolactoferrin, a related iron protein. The crystallog. data reveals that binding of both complexes takes place at histidine residues, and that the ligand (indazole) remains bound in the case of HInd[RuInd2Cl4].
IT **103875-27-0 142388-45-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antitumor Ru(III) complexes binding to human apotransferrin and apolactoferrin)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

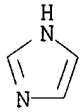
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

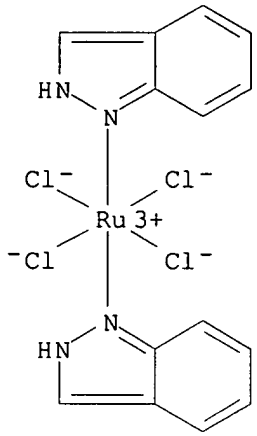
CRN 288-32-4
CMF C3 H4 N2



RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

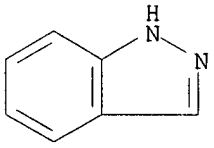
CRN 142388-44-1
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 33 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:124397 HCAPLUS
DN 120:124397
TI The binding properties of two antitumor ruthenium(III) complexes to apotransferrin
AU Kratz, Felix; Hartmann, Markus; **Keppler, Bernhard**; Messori, Luigi
CS Dep. Chem., Univ. Florence, Florence, 50121, Italy
SO Journal of Biological Chemistry (**1994**), 269(4), 2581-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The interaction of two ruthenium(III) complexes exhibiting high anticancer activity, namely trans-indazolium(bisindazole)tetrachlororuthenate(III) (I) and trans-imidazolium(bisimidazole)tetrachlororuthenate(III) (II), with human serum apotransferrin has been investigated through spectroscopic and chromatog. techniques with the ultimate goal of preparing adducts with good selectivity for cancer cells. Whereas the binding of II to human serum apotransferrin takes several hours, I, the less toxic complex, gives rise to a well defined 2:1 complex within a few minutes. The authors have ascertained that I binding occurs around the iron binding sites; binding does not occur in the absence of bicarbonate, and this

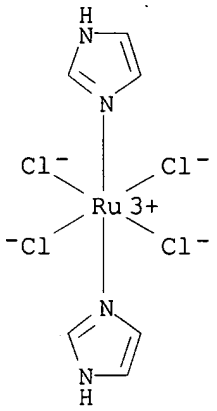
anion dictates the kinetic and mechanistic characteristics of protein binding of I. The two ruthenium(III) complexes do not behave as iron(III) complexes, e.g. Fe(EDTA) or Fe(nitrilotriacetate), which lose their resp. ligands when binding apotransferrin, but the N-heterocycles remain attached to the metal in the protein-bound species. Reversion of binding is obtained by acidification in the presence of chelators such as citrate or ATP. In comparison with cisplatin and its deactivation by serum proteins, the authors' results indicate that other metal complexes such as I could use transferrin as a drug delivery system. Furthermore, the rapid protein binding of I seems to be related to a lower toxicity while still exhibiting high antitumor activity.

IT **103875-27-0 124875-20-3**
RL: PROC (Process)
(binding of, to apotransferrin)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

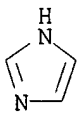
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

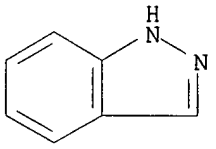
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

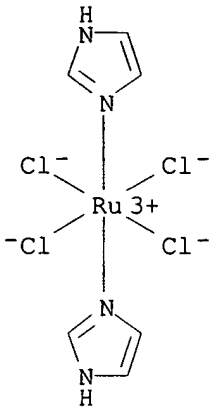
CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 34 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:94941 HCAPLUS
DN 120:94941
TI Kinetic, spectroscopic and LPLC studies of the interactions of antitumor ruthenium(III) complexes with serum proteins
AU Kratz, F.; Mulinacci, N.; Messori, L.; Bertini, I.; **Keppler, B. K.**
CS Anorg. Chem. Inst., Univ. Heidelberg, Heidelberg, 6900/1, Germany
SO Met. Ions Biol. Med., Proc. Int. Symp., 2nd (**1992**), 69-74.
Editor(s): Anastassopoulou, Jane. Publisher: Libbey, Montrouge, Fr.
CODEN: 59OJAL
DT Conference
LA English
AB Trans-Indazolium-bisindazole-tetrachlororuthenate(III) (ru-ind) reacts with serum and new Ru(III) species are formed which react rapidly with serum proteins. A major amount of Ru-ind is bound to albumin and a small amount is bound to transferrin. The binding is rapid and depends on pH and HCO3-. The binding and antitumor properties of trans-Imidazolium-bisimidazole-tetrachlororuthenate (III) (ICR) are also examined and compared with those of ru-ind. The higher antitumor activity of ru-ind, compared to ICR may be related to its rate of reaction with serum proteins.
IT **103875-27-0 142388-45-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with proteins of blood serum)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

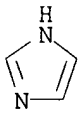
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

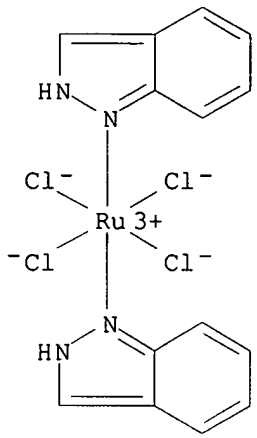
CRN 288-32-4
CMF C3 H4 N2



RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

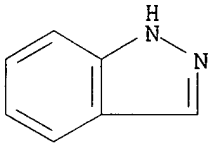
CRN 142388-44-1
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 35 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:456146 HCAPLUS
DN 119:56146
TI Formulation of water- or lipid-soluble transition metal compounds for use in antitumor therapy and for stimulation of the hematopoietic system
IN Reszka, Regina; Fichtner, Iduna
PA Max-Delbrueck-Centrum fuer Molekulare Medizin Berlin-Buch, Germany
SO Ger. Offen., 5 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 4134158	A1	19930415	DE 1991-4134158	19911011 <--
	DE 4134158	C2	19970213		
	WO 9306824	A1	19930415	WO 1992-DE868	19921009 <--
	W: AU, BG, BR, CA, CS, FI, HU, JP, KR, NO, PL, RO, RU, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
	AU 9227551	A1	19930503	AU 1992-27551	19921009 <--
	EP 611303	A1	19940824	EP 1992-921289	19921009 <--
	EP 611303	B1	19980527		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE

JP 08508237	T2	19960903	JP 1993-506551	19921009	<--
JP 3627240	B2	20050309			
AT 166576	E	19980615	AT 1992-921289	19921009	<--
ES 2118831	T3	19981001	ES 1992-921289	19921009	<--
US 5620703	A	19970415	US 1994-221017	19940331	<--
PRAI DE 1991-4134158	A	19911011	<--		
WO 1992-DE868	A	19921009	<--		

OS MARPAT 119:56146

AB The title transition metal compds. are formulated as liposomes with an amphiphile (lipid, surfactant, or emulsifying agent), a steroid, a charged lipid, and a carrier liquid Thus, a film of egg phosphatidylcholine 2328 and cholesterol 1132 mg was dispersed in a mixture of 450 mL THF and 60 mL sterile Ca-free phosphate-buffered saline (pH 7.2-7.4) containing 900 mg carboplatin, the THF was removed under vacuum, and the resulting liposomes were separated from nonencapsulated carboplatin by centrifugation, resuspended in buffer, and extruded through successively smaller-pored filter membranes (2.0, 1.0, 0.8, 0.4, and 0.2 μm) to provide a suspension for i.v. administration.

IT **124875-20-3**
RL: BIOL (Biological study)
(liposomes containing, as neoplasm inhibitor)

RN 124875-20-3 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

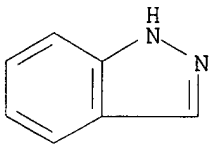
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 36 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:225067 HCAPLUS
DN 118:225067
TI Antineoplastic activity of three ruthenium derivatives against chemically induced colorectal carcinoma in rats
AU Seelig, Matthias H.; Berger, Martin R.; **Keppler, Bernhard K.**
CS Inst. Toxicol. Chemotherapy, German Cancer Res. Cent., Heidelberg, W-6900, Germany
SO Journal of Cancer Research and Clinical Oncology (**1992**), 118(3), 195-200
CODEN: JCROD7; ISSN: 0171-5216
DT Journal

LA English

AB The antineoplastic activity of the ruthenium complexes trans-imidazolium[tetrachlorobisimidazoleruthenate(III)], HIm(RuIm2Cl4), trans-indazolium[tetrachlorobis(1H-indazole)ruthenate(III, N2)], HInd [RuInd2Cl4(N2)], and trans-indazolium[tetrachlorobis(2H-indazole)ruthenate(III,N1)], HInd[RuInd2Cl4-(N1)] was assessed in acetoxymethylmethylnitrosamine-induced autochthonous colorectal carcinomas of Sprague-Dawley rats. The model is not sensitive to clin. established antineoplastic agents, including cisplatin. An exception is the combination therapy with 5-fluorouracil/leucovorin, which shows moderate activity against the tumor model. In contrast to this general trend, the new substances were all active against this tumor. HIm(RuIm2Cl4) was very effective at all dosages applied (7.5 mg/kg, 5.3 mg/kg, and 3.8 mg/kg), as indicated by percentage treated/control (T/C values of 23%, 34.5% and 44%. Toxicity was considerable as shown by a body weight change of -30%, -19%, and -9%. Nevertheless, the medium dose seems to be the optimum in terms of mortality (0% vs 15% in the control group), whereas at the highest dose, mortality increased as a result of substance toxicity, and at the lowest dose mortality increased through tumor growth combined with substance toxicity. HInd[RuInd2Cl4(N2)] showed high efficacy at the highest dosage of 13 mg/kg, reaching a T/C value of 27% combined with 0% mortality vs. 15% in the control group. In equimolar dosages (10 mg/kg, 7.1 mg/kg and 5.1 mg/kg), the compound is not as active as HIm-(RuIm2Cl4), as indicated by T/C values of 50.2%, 45.7%, and 38.6%. HInd[RuInd2Cl4(N1)] was slightly but not significantly better than Hind[RuInd2Cl4(N2)] at a dosage of 7.1 mg/kg and is advantageous over combination therapy with 5-fluorouracil and leucovorin (20/20 mg/kg) in terms of efficacy (T/C = 37.6% vs. 44.7%) and mortality (6% vs. 33.3%).

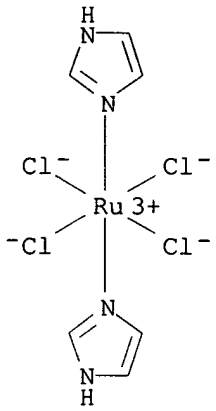
IT **103875-27-0 124875-20-3 142388-45-2**
RL: BIOL (Biological study)
(colorectal carcinoma inhibition by)

RN 103875-27-0 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

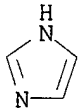
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

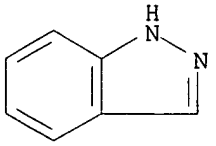
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

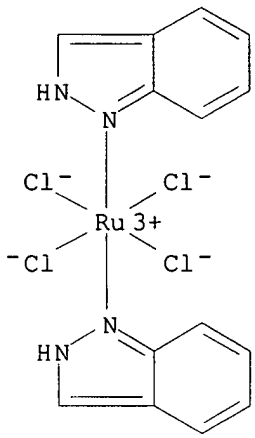
CRN 271-44-3
CMF C7 H6 N2



RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

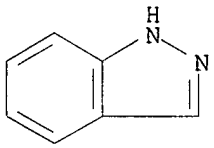
CRN 142388-44-1
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 37 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:462485 HCAPLUS
DN 117:62485
TI Antitumor activity of some ruthenium derivatives in human colon cancer cell lines in vitro
AU Galeano, A.; Berger, M. R.; **Keppler, B. K.**
CS Inst. Toxicol. Chemother., Ger. Cancer Res. Cent., Heidelberg, Germany
SO Arzneimittel-Forschung (**1992**), 42(6), 821-4
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
AB Six ruthenium derivs. were evaluated in vitro in two human colon cancer

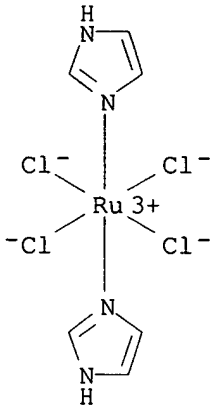
cell lines (SW707 and SW948) utilizing the microculture tetrazolium test (MTT) and cell counting with a Coulter Counter. The ruthenium compound sodium (tetrachloroimidazoledimethylsulfoxideruthenate)-bisdimethylsulfoxide (Na(RuDMSOimCl4)) showed the best efficacy in inhibiting cell proliferation of both colon cancer cell lines followed by the other DMSO ruthenium compound sodium (tetrachloroindazoledimethylsulfoxideruthenate)-bisdimethylsulfoxide (Na(RuDMSOIndCl4)), as demonstrated by IC50 values (80 and 90 μg/mL in SW707 and SW948 cell lines for Na(RuDMSOImCl4); 155 and 165 μg/mL in SW707 and SW948 cell lines for Na(RuDMSOIndCl4), resp.). Of the ruthenium derivs. without DMSO, transindazolium-[tetrachlorobis(1H-indazole)ruthenate (III,N2)] (HInd[RuInd2Cl4(N2)]), was as active as its DMSO-containing congener whereas trans-imidazolium[tetrachlorobisimidazoleruthenate)(III)] (HIm(RuIm2Cl4)) was less active, as shown by the IC50 values: (HIm (RuIm2Cl4) = 250 and 260 μg/mL in cell lines SW707 and SW948; HInd[RuInd2Cl4(N2)] = 110 and > 200 μg/mL in cell lines SW707 and SW948, resp.). The other ruthenium derivs. containing pyrazole and triazole as ligands (trans-pyrazolium (tetrachlorobispyrazoleruthenate) (III), PzH(RuPz2Cl4) and triazolium(tetrachlorobistriazoleruthenate) (III), TrH(RuTr2Cl4)) were active only at high concns. that cannot be regarded as realistic in vivo, as shown by the resp. IC50 values: (PzH(RuPz2Cl4) = 1056 and 750 μg/mL in cell lines SW707 and SW948; TrH(RuTr2Cl4) = 350 and 300 mg/mL in cell lines SW707 and SW948). The promising activity of ruthenium compds. with DMSO, indazole and imidazole as ligands should be evaluated in vivo for elucidating their possible role in the treatment of colorectal cancer.

IT **103875-27-0 124875-20-3 124951-57-1**
135212-15-6
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of, in human colon cancer cell lines)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

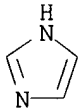
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

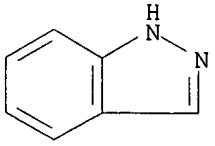
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

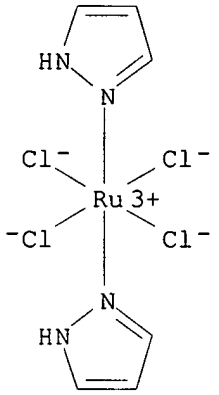
CRN 271-44-3
CMF C7 H6 N2



RN 124951-57-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-pyrazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-pyrazole (1:1) (9CI) (CA INDEX NAME)

CM 1

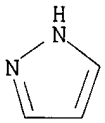
CRN 124951-56-0
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

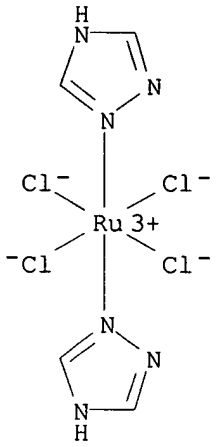
CRN 288-13-1
CMF C3 H4 N2



RN 135212-15-6 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-1,2,4-triazole-κN2)-, (OC-6-22)-, hydrogen, compd. with 1H-1,2,4-triazole (1:1) (9CI) (CA INDEX NAME)

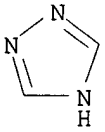
CM 1

CRN 135212-14-5
CMF C4 H6 Cl4 N6 Ru . H
CCI CCS



CM 2

CRN 288-88-0
CMF C2 H3 N3



L77 ANSWER 38 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:439922 HCAPLUS
DN 117:39922
TI Synergistic antitumor interactions between newly synthesized ruthenium complexes and cytokines in human colon carcinoma cell lines
AU Kreuser, Ernst D.; **Keppler, Bernhard K.**; Berdel, Wolfgang E.; Piest, Almuth; Thiel, Eckhard
CS Klin. Steglitz, Free Univ. Berlin, Berlin, 1000/45, Germany
SO Seminars in Oncology (**1992**), 19(2, Suppl. 3), 73-81
CODEN: SOLGAV; ISSN: 0093-7754
DT Journal
LA English
AB The purpose of these studies was to assess the antiproliferative properties of newly synthesized, heterocyclic ruthenium complexes alone and in combination with cytokines (tumor necrosis factor-α, interferon α, β, γ) against various human colon carcinoma cell lines. To determine whether any of these ruthenium compds. possesses antitumor activity and reveals synergistic interaction with cytokines six new ruthenium complexes were studied. All six compds. exerted concentration-dependent antitumor effects in all colon cancer cell lines tested.
The most effective compds. were transindazolium[tetrachloro[2H-

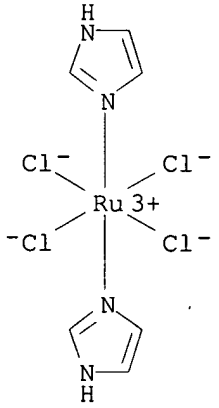
indazole)ruthenate (III, N1)] and trans-indazolium[tetrachlorobis(1H-indazole)ruthenate (III, N2)]. Interferon α, β, γ, as well as, tumor necrosis factor-α exerted only minimal antiproliferative effects in colon carcinoma cell lines. The data were further analyzed to determine whether preincubation with cytokines altered sensitivity of the cells to synergistically potentiating growth-inhibitory effects. Although simultaneous incubation of ruthenium complexes and interferon did not result in synergistic or additive interactions, 24-h preincubation with interferon α, β, γ significantly enhanced antitumor activity. The authors conclude from these data that two of six newly synthesized ruthenium complexes possess antiproliferative activity against a panel of human colon carcinoma cell lines. Moreover, biol. modulation with interferon using 24-h preincubation resulted in synergistic interactions.

IT **103875-27-0 124875-20-3 135212-15-6 142388-45-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(neoplasm-inhibiting activity of, cytokines synergism with, in human cells)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

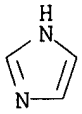
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

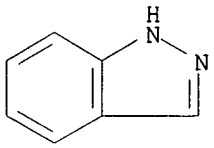
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

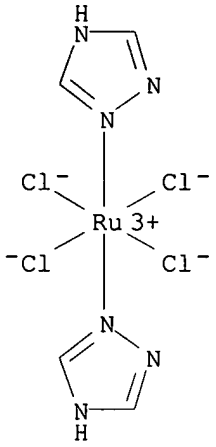
CRN 271-44-3
CMF C7 H6 N2



RN 135212-15-6 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-1,2,4-triazole-κN2)-, (OC-6-22)-, hydrogen, compd. with 1H-1,2,4-triazole (1:1) (9CI) (CA INDEX NAME)

CM 1

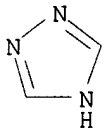
CRN 135212-14-5
CMF C4 H6 Cl4 N6 Ru . H
CCI CCS



● H^+

CM 2

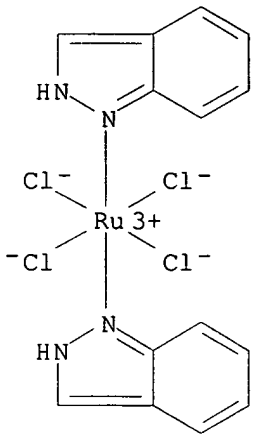
CRN 288-88-0
CMF C2 H3 N3



RN 142388-45-2 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2H-indazole-κN1)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

CM 1

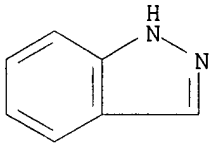
CRN 142388-44-1
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 39 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:187595 HCAPLUS
DN 116:187595
TI Studies on the antitumor activity of platinum and ruthenium complexes
AU Sakai, Kazuo; Yamane, Yasuhiro
CS Fac. Pharm. Sci., Chiba Univ., Chiba, 260, Japan
SO Biomedical Research on Trace Elements (**1990**), 1(1), 59-64
CODEN: BRTEE5; ISSN: 0916-717X
DT Journal
LA Japanese
AB Platinum complexes such as cis-diaminedichloroplatinum (II) (CDDP) and 1,2-diaminocyclohexanedichloroplatinum(II) (DACH·DP) are known to be potent antitumor agents. In the present study, cis-diammine(ascorbato)platinum(II) (CDAP) and 1,2-diaminocyclohexane(ascorbato)platinum(II) (DACH·AP) in which the chlorides of CDDP and DACH·DP are replaced with the ascorbates, were examined The ascorbatoplatinum complexes were found to be more water-soluble than the chloride complexes. The inhibitory effect of platinum complexes treatment on the incorporation of thymidine into the DNA of the liver and lung of rats treated with diethylnitrosamine (DEN) was examined in relation to the antitumor activity. Not only CDDP and DACH·DP but also CDAP and DACH·AP exerted strong inhibitory effects on the DNA

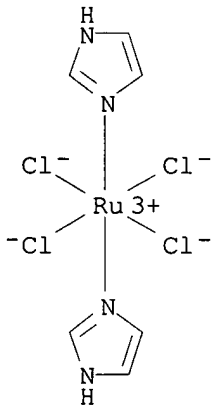
synthesis in the liver and lung. The antitumor activity of imidazolium-bisimidazoleelectrachlororuthenium(III)(ICR) against P388 leukemia cells in vivo has been reported to be as potent as that of CDDP. ICR and imidazolium-bisimidazole(diascorbato)ruthenium(III) (IAR) were therefore compared with CDDP and CDAP. The inhibitory effects of the ruthenium complexes treatment on the incorporation of thymidine into DNA of liver and lung of rats treated with DEN were examined The inhibitory effect of ICR and IAR was found to be weaker than that of CDDP and CDAP. The antitumor activities of ICR and IAR against L1210 leukemia cells in vivo were also much weaker than those of CDDP and CDAP. IAR was more water-soluble than ICR, but the toxicity was not decreased. IAR had less antitumor activity.

IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(neoplasm-inhibiting activity of, DNA formation inhibition in relation to)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

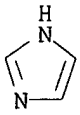
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

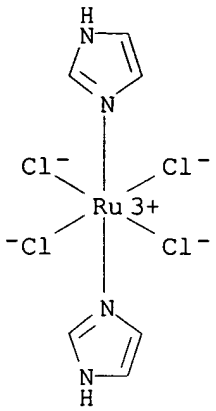
CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 40 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:670152 HCAPLUS
DN 115:270152
TI Inhibition of Escherichia coli DNA polymerase I catalyzed DNA polymerization by trans-imidazolium-bisimidazoletetrachlororuthenate(III)
AU Holler, E.; Schaller, W.; **Keppler, B.**
CS Inst. Biophys. Phys. Biochem., Univ. Regensburg, Regensburg, W-8400, Germany
SO Arzneimittel-Forschung (**1991**), 41(10), 1065-8
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
AB The tumor-inhibiting metal complex trans-imidazolium-bisimidazoletetrachloruthenate(III) (ICR) reacts with DNA and inhibits template-primer properties for DNA synthesis catalyzed by E. coli DNA polymerase I. The reaction with DNA depends on the aging (half-life 6.8 h) of the aqueous solution containing ICR. The kinetics of the reaction with DNA are reminiscent of those for cisplatin.
IT **103875-27-0**
RL: BIOL (Biological study)
(DNA polymerase of Escherichia coli inhibition by, antitumor effects in relation to)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

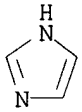
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 41 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:505583 HCAPLUS
DN 115:105583
TI New platinum, titanium, and ruthenium complexes with different patterns of DNA damage in rat ovarian tumor cells
AU Fruehauf, S.; Zeller, W. J.
CS Inst. Toxicol. Chemother., Ger. Cancer Res. Cent., Heidelberg, 6900, Germany
SO Cancer Research (**1991**), 51(11), 2943-8
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB DNA protein cross-links (DPC), DNA interstrand cross-links (ISCL), and DNA single strand breaks following treatment of exptl. ovarian tumor cells (0-342) with five new metal complexes (three platinum, one titanium, one ruthenium compds.) were investigated at 6, 24, and 48 h after drug exposure and compared with their in vitro growth inhibitory potential. Cisplatin (DDP) served as reference drug. The following new compds. were tested: 18-crown-6-tetracarboxybis-diammineplatinum(II) (CTDP), cis-aminotrismethylenephosphonato-diammineplatinum(II) (AMDP), cis-diamminecyclohexano-aminotrismethylenephosphonato-platinum(II) (DAMP), diethoxybis-(1-phenylbutane-1,3-dionato)-titanium(IV)(budotitane), and trans-indazolium-tetrachlorobisindazole-ruthenate(III) (IndCR). At equimolar concns. DNA crosslinking activity of the platinum agents

decreased in the order cisplatin, CTDP, AMDP, DAMP: this was paralleled by growth inhibition in a cell proliferation assay. CTDP-induced interstrand crosslinking occurred more slowly compared to cisplatin (DDP) (6 h: CTDP, 73 vs. DDP, 365 rad equivalent), but reached a peak similar to cisplatin 24 h after exposure (CTDP, 317 vs. DDP, 392 rad equivalent). At this time point in contrast to DDP no DNA protein cross-links were observed for CTDP (total cross-links: CTDP 310, DDP 1987 rad equivalent). Thus, at 24 h, CTDP was found to be distinctly less reactive to proteins than DDP, and it is suggested that CTDP might be similar in its toxicity pattern to the structurally related compound carboplatin which was also reported to be less reactive to protein than DDP. By 48 h, CTDP- and DDP-induced interstrand cross-links were 65 and 180 rad equivalent, resp. Although at a lower level, by 24 h, AMDP showed a ratio of ISCL to total cross-links (179 vs. 213 rad equivalent), which was comparable to CTDP. The second biphosphonate complex DAMP was the least active platinum compound in terms of DNA damage, effecting only 16 rad equivalent ISCL and 63 rad equivalent total cross-links; similar to DDP, DAMP displayed a higher DPC fraction at 24 h. The titanium complex diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV) showed dose-dependent inhibition of cell proliferation, while no significant DNA damage could be detected with the alkaline elution technique. These results, together with observations from other authors, indicating that space-filling planar aromatic ring systems are important for its antitumor activity, suggest as possible mechanism of action of diethoxybis-(1-phenylbutane-1,3-dionato)-titanium(IV) intercalation into the DNA. Following administration of the ruthenium compound IndCR only few ISCL and DPC were observed with a maximum at 6 h (ISCL, 15; total cross-links, 49 rad equivalent); thereafter both lesions were declining. Further studies on the mechanism of action of this class of antitumor agents should take into account that in hypoxic tumor tissue the Ru(III)-ion of IndCR might be reduced to Ru(II) which is known to be more reactive to DNA.

IT **124875-20-3**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(DNA damage from, in ovarian tumors, structure in relation to)
RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

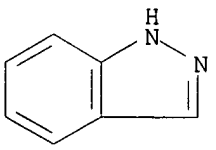
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2

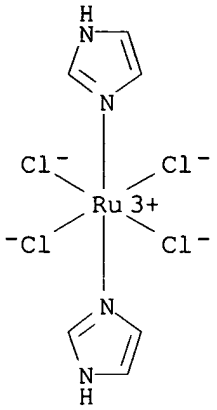


L77 ANSWER 42 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1991:464190 HCAPLUS
DN 115:64190
TI Antineoplastic effects of mer-trichlorobisdimethylsulfoxideaminoruthenium II against murine tumors: comparison with cisplatin and with ImH[RuIm2Cl4]
AU Pacor, Sabrina; Sava, Gianni; Ceschia, Valentina; Bregant, Francesca; Mestroni, Giovanni; Alessio, Enzo
CS Sch. Pharm., Univ. Trieste, Trieste, 34127, Italy
SO Chemico-Biological Interactions (**1991**), 78(2), 223-34
CODEN: CBINA8; ISSN: 0009-2797
DT Journal
LA English
AB An asym. ruthenium III complex containing dimethylsulfoxide ligands, namely mer-trichlorobisdimethylsulfoxideaminoruthenium III (BBR2382), has been tested in mice bearing solid metastasizing tumors. The effects of i.p. treatment with BBR2382 on primary tumor growth and on the survival time of hosts carrying s.c. or i.m. tumors have been compared to those of cisplatin and of a ruthenium III complex with imidazole ligands, ImH[RuIm2Cl4], described as a potent antitumor agent in a number of exptl. models of murine neoplasms. In mice bearing Lewis lung carcinoma, BBR2382 results as effective as cisplatin on s.c. primary tumor growth and more potent than cisplatin on the prolongation of host survival time. The combined treatment of mice bearing Lewis lung carcinoma with cisplatin and BBR2382 causes a reduction of s.c. tumors higher than that caused by each single agent; the effects on host survival time are similar to those caused by BBR2382 alone but significantly superior to those caused by cisplatin alone. In CBA mice bearing MCa mammary carcinoma, the effects of BBR2382 are slightly lower than those of cisplatin on i.m. tumors but are equivalent on host survival time. The comparison of the antineoplastic action of BBR2382 with that of ImH[RuIm2Cl4] is always in favor of the former, independently of the parameter chosen and of the tumor system used. Qual., the antitumor action of BBR2382 seems different from that of cisplatin and of ImH[RuIm2Cl4]; it is supposed that this agent, like other ruthenium III dimethylsulfoxide complexes, could have a particular efficacy for tumors localized in the lungs.
IT **103875-27-0**
RL: BIOL (Biological study)
(neoplasm inhibition by trichlorobisdimethylsulfoxideaminoruthenium vs.)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

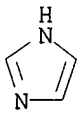
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 43 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:464143 HCAPLUS
DN 115:64143
TI In vitro evaluation of platinum, titanium and ruthenium metal complexes in cisplatin-sensitive and -resistant rat ovarian tumors
AU Fruehauf, S.; Zeller, W. J.
CS Inst. Toxicol. Chemother., Ger. Cancer Res. Cent., Heidelberg, W-6900, Germany
SO Cancer Chemotherapy and Pharmacology (**1991**), 27(4), 301-7
CODEN: CCPHDZ; ISSN: 0344-5704
DT Journal
LA English
AB The antitumor activity of eight new metal complexes (three platinum, one titanium, four ruthenium derivs.) was investigated in a cisplatin (DDP) - sensitive (O-342) and a DDP-resistant (O-342/DDP) ovarian tumor line using the bilayer soft-agar assay. A continuous exposure set up at logarithmically spaced concns. was used to test the drugs; to uncover possible pharmacokinetics features, a short-term exposure was addnl. included for selected compds. DDP served as the reference drug. The following compds. were investigated: 18-crown-6-tetracarboxybisdiammineplatinum(II) (CTDP), cis-aminotrismethylenephosphonatodiammineplatinum(II) (ADP), cis-diamminecyclohexanoaminotrismethylenephosphonatoplatinum(II) (DAP), diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV) (DBT, budotitane), trans-imidazoliumbisimidazoletetrachlororuthenate(III) (ICR),

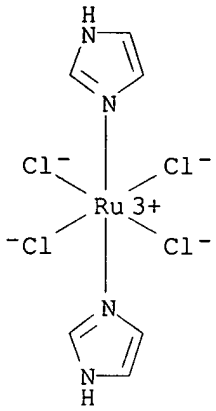
trans-indazoliumtetrachlorobisindazoleruthenate(III) (IndCR), cis-triazoliumtetrachlorobistriazoleruthenate(III) (TCR) and trans-pyrazoliumtetrachlorobispyrazoleruthenate(III) (PCR). Of the new metal complexes, CTDP was the most active compound in O-342, resulting in a percentage of control plating efficiency of 1, 12, and 40 following continuous exposure to 10, 1, and 0.1 μM, resp., and was thus comparable to DDP at equimolar concns. In the resistant line, 10 μM CTDP reduced colony growth to 18%, whereas an equimolar concentration of DDP effected a reduction to 26%. During short-term exposure, CTDP was inferior to DDP, which may be ascribed to the stability of the bis-dicarboxylate platinum ring system. The titanium compound DBT, in contrast, showed promising effects at its highest concentration (100 μM) during short-term exposure in both lines; at this concentration the activity in O-342/DDP was higher than that in O-342 (7% vs. 34% of control plating efficiency at 100 μM). All ruthenium complexes showed higher activity in the resistant line O-342/DDP than in the sensitive counterpart. ICR was the most active compound Following continuous exposure of O-342/DDP cells to 10 μM ICR, colony growth was reduced to 18% that of controls. Further studies should concentrate on CTDP and ICR for the following reasons: the activity of CTDP was equal to that of DDP at equimolar concns. during continuous exposure; considering that the in vivo toxicity of DDP was 3-fold that of CTDP, an increase in the therapeutic index of CTDP would be expected. ICR showed the best effect of all ruthenium complexes; it was superior to DDP in the resistant line.

IT **103875-27-0 124951-57-1 135212-15-6**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(neoplasm inhibition by, in cisplatin-resistant vs. -sensitive ovarian tumor lines)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

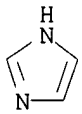
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

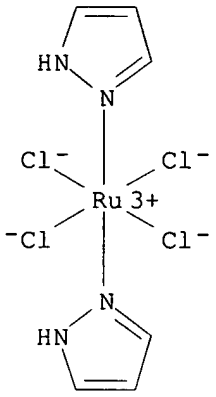
CRN 288-32-4
CMF C3 H4 N2



RN 124951-57-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-pyrazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-pyrazole (1:1) (9CI) (CA INDEX NAME)

CM 1

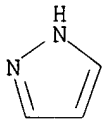
CRN 124951-56-0
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

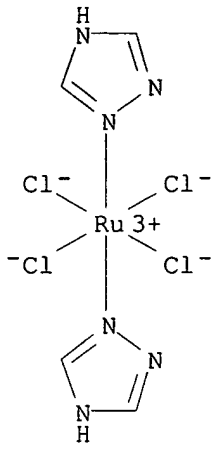
CRN 288-13-1
CMF C3 H4 N2



RN 135212-15-6 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-1,2,4-triazole-κN2)-, (OC-6-22)-, hydrogen, compd. with 1H-1,2,4-triazole (1:1) (9CI) (CA INDEX NAME)

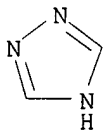
CM 1

CRN 135212-14-5
CMF C4 H6 Cl4 N6 Ru . H
CCI CCS



CM 2

CRN 288-88-0
CMF C2 H3 N3



L77 ANSWER 44 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:441400 HCAPLUS
DN 115:41400
TI Antitumor action of mer-trichlorobis(dimethyl sulfoxide)aminoruthenium(III) (BBR2382) in mice bearing Lewis lung carcinoma
AU Pacor, S.; Sava, G.; Bregant, F.; Ceschia, V.; Alessio, E.; Mestroni, G.
CS Sch. Pharm., Univ. Trieste, Trieste, I-34127, Italy
SO Met. Ions Biol. Med., Proc. Int. Symp., 1st (**1990**), 482-4.
Editor(s): Collery, Philippe. Publisher: Libbey, Paris, Fr.
CODEN: 56ZJAL
DT Conference
LA English
AB The differential effects of i.p. treatment of BD2F1 female mice carrying s.c. implants of Lewis lung carcinoma with mer-trichlorobis(DMSO)aminoruthenium(III), BBR2382, on primary tumor growth and on host survival time, were compared to those of equitoxic doses of cis-dichlorodiammineplatinum (cisplatin) and of imidazoliumbis(imidazole)tetrachlororuthenate [ImH(RuIm2Cl4)]. BBR2382 significantly reduces primary tumor growth by a factor comparable to that of cisplatin but significantly larger than that of ImH(RuIm2Cl4). Similar results are obtained in terms of increase of survival time which is

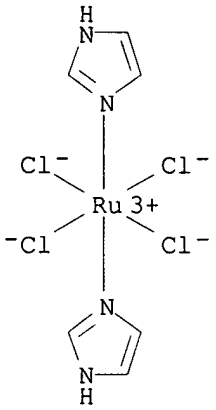
prolonged by 33%; this parameter is significantly better for mice treated with BBR2382 than for those treated with cisplatin. These data suggest the existence of antimetastatic effects and stress the potential therapeutic usefulness of ruthenium(III)dimethyl sulfoxides in cancer treatment.

IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(antitumor activity of trichlorobis(DMSO)aminoruthenium in relation to)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

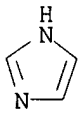
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

CRN 288-32-4
CMF C3 H4 N2

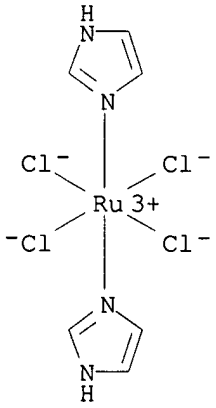


L77 ANSWER 45 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:421720 HCAPLUS
DN 115:21720
TI Chemoresistance in rat ovarian tumors
AU Zeller, W. J.; Fruhauf, S.; Chen, G.; **Keppler, B. K.**; Frei, E.;

Kaufmann, M.
CS Inst. Toxicol. Chemotherapy, German Cancer Res. Cent., Heidelberg, Germany
SO European Journal of Cancer (**1991**), 27(1), 62-7
CODEN: EJCAEL; ISSN: 0959-8049
DT Journal
LA English
AB In a cisplatin resistant subline (O-342/DPP) of an i.p. growing transplantable rat ovarian tumor (O-342), intracellular glutathione (GSH) was approx. doubled. GSH reductase activity was higher, although no difference was found for GSH-S-transferase. Twenty-four h after exposure to cisplatin, formation of DNA interstrand cross-links was at a maximum in both lines and significantly higher in O-342. Combination treatment of O-342/DDP with buthionine sulfoximine plus cisplatin resulted in a marginal increase in survival compared with cisplatin treatment; treatment of this line with 3-aminobenzamide plus cisplatin was also superior to cisplatin alone. In the sensitive line, both combinations were likewise superior to cisplatin alone. In vitro, at equimolar concentration, a new platinum complex (CTDP) was at least as active as cisplatin in both lines, which suggests a superior therapeutic index because its LD50 in mice is threefold higher than that of cisplatin. A ruthenium complex (ICR) had a higher activity in the resistant line. A titanium complex (budotitane) was not active.
IT **103875-27-0**
RL: BIOL (Biological study)
(neoplasm inhibition by cisplatin and, resistance in)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

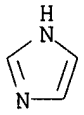
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

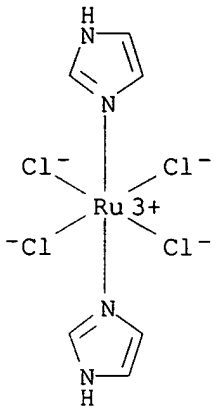
CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 46 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:240056 HCAPLUS
DN 114:240056
TI Efficacy of two ruthenium complexes against chemically induced autochtonous colorectal carcinoma in rats
AU Seelig, M. H.; Berger, M. R.; **Keppler, B. K.**; Schmaehl, D.
CS Inst. Toxicol. Chemother., Ger. Cancer Res. Cent., Heidelberg, 6900, Germany
SO Met. Ions Biol. Med., Proc. Int. Symp., 1st (**1990**), 476-8.
Editor(s): Collery, Philippe. Publisher: Libbey, Paris, Fr.
CODEN: 56ZJAL
DT Conference
LA English
AB trans-Indazoliumbisindazoletetrachlororuthenate (III) and trans-imidazoliumbisimidazoletetrachlororuthenate (III) showed tumor growth inhibition in chemical induced colorectal carcinoma in rats.
IT **103875-27-0 124875-20-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of, against chemical induced autochtonous colorectal carcinoma)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

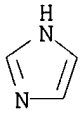
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

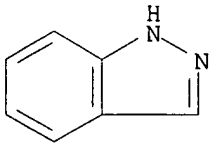
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

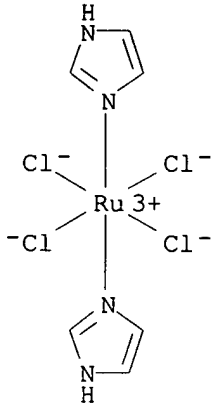
CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 47 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1990:69481 HCAPLUS
DN 112:69481
TI New ruthenium complexes for the treatment of cancer
AU **Keppler, B. K.**; Henn, M.; Juhl, U. M.; Berger, M. R.; Niebl, R.; Wagner, F. E.
CS Anorg. Chem. Inst., Univ. Heidelberg, Heidelberg, 6900, Fed. Rep. Ger.
SO Progress in Clinical Biochemistry and Medicine (**1989**), 10(Ruthenium Other Non-Platinum Met. Complexes Cancer Chemother.), 41-69
CODEN: PCBMEM; ISSN: 0177-8757
DT Journal
LA English
AB The aim of developing new tumor-inhibiting ruthenium complexes, in particular compds. which act against tumors that are chemoresistant, led to the synthesis of different classes of ruthenium complexes. Ruthenium complexes were selected for further evaluation on the basis of the increase in survival time in the P388 tumor model and water solubility The water-soluble ruthenium complexes coordinated with heterocyclic ligands in the trans-position, HB(RuB2Cl4), and the corresponding pentachloro derivs., (HB)2(RuBCl5), were identified as being the most active complexes. Chemical properties were investigated by means of x-ray analyses, Moessbauer spectra, NMR spectra, and other methods. Galenic formulation was established based on solubility in water or physiol. saline. Stability of the complexes was sufficient for infusion therapy. The antitumor activity of such compds. was confirmed not only in the P388 tumor model but also in the Walker 256 carcinosarcoma, the Stockholm ascitic tumor, the s.c. growing B 16 melanoma, the i.m. sarcoma 180 and the acetoxymethylmethylnitrosamine-induced colorectal tumors of the rat. The compds. ImH(RuIm2Cl4) and IndH(RuInd2Cl4) [Im = imidazole; Ind = indazole] were highly active against these tumor models and were selected for toxicol. study.
IT **103875-27-0P 105085-46-9P 105085-50-5P**
105085-56-1P 110649-85-9P 111137-60-1P
111137-62-3P 124875-10-1P 124875-14-5P
124875-16-7P 124875-18-9P 124875-20-3P
124951-57-1P
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as neoplasm inhibitor)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

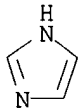
CM 1

CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



CM 2

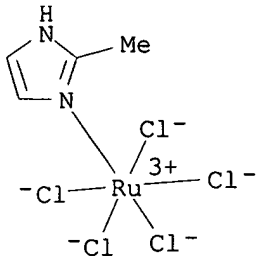
CRN 288-32-4
CMF C3 H4 N2



RN 105085-46-9 HCAPLUS
CN Ruthenate(2-), pentachloro(2-methyl-1H-imidazole-κN3)-, (OC-6-21)-, dihydrogen, compd. with 2-methyl-1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

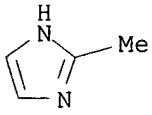
CRN 105085-45-8
CMF C4 H6 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

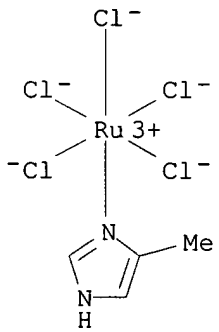
CRN 693-98-1
CMF C4 H6 N2



RN 105085-50-5 HCAPLUS
CN Ruthenate(2-), pentachloro(4-methyl-1H-imidazole-N3)-, (OC-6-21)-, dihydrogen, compd. with 4-methyl-1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

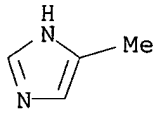
CRN 105085-49-2
CMF C4 H6 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

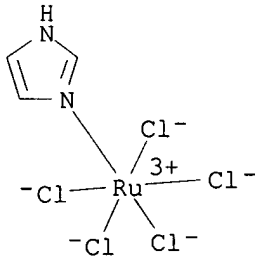
CRN 822-36-6
CMF C4 H6 N2



RN 105085-56-1 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-imidazole-N3)-, (OC-6-21)-, dihydrogen, compd. with 1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

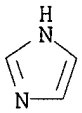
CRN 105085-55-0
CMF C3 H4 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2

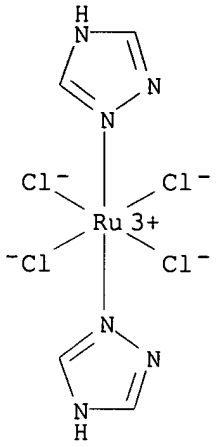


RN 110649-85-9 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-1,2,4-triazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-1,2,4-triazole (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 110649-84-8
CMF C4 H6 Cl4 N6 Ru . H

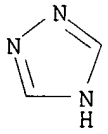
CCI CCS



● H^+

CM 2

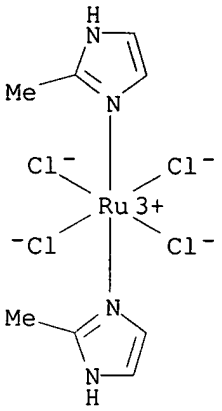
CRN 288-88-0
CMF C2 H3 N3



RN 111137-60-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2-methyl-1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 2-methyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

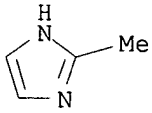
CM 1

CRN 111137-59-8
CMF C8 H12 Cl4 N4 Ru . H
CCI CCS



CM 2

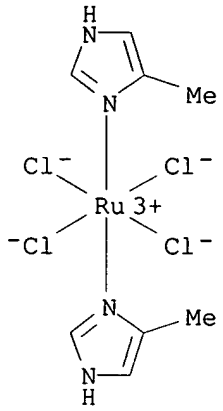
CRN 693-98-1
CMF C4 H6 N2



RN 111137-62-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(4-methyl-1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 4-methyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

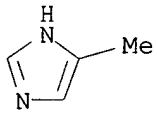
CRN 111137-61-2
CMF C8 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

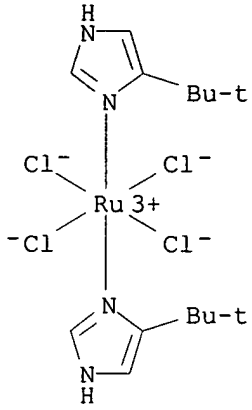
CRN 822-36-6
CMF C4 H6 N2



RN 124875-10-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis[4-(1,1-dimethylethyl)-1H-imidazole-N3]-, (OC-6-11)-, hydrogen, compd. with 4-(1,1-dimethylethyl)-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

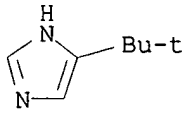
CRN 124875-09-8
CMF C14 H24 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

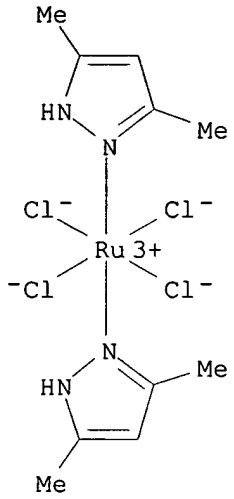
CRN 21149-98-4
CMF C7 H12 N2



RN 124875-14-5 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(3,5-dimethyl-1H-pyrazole-N2)-, (OC-6-11)-, hydrogen, compd. with 3,5-dimethyl-1H-pyrazole (1:1) (9CI) (CA INDEX NAME)

CM 1

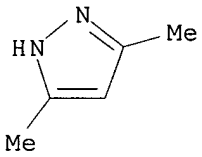
CRN 124875-13-4
CMF C10 H16 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

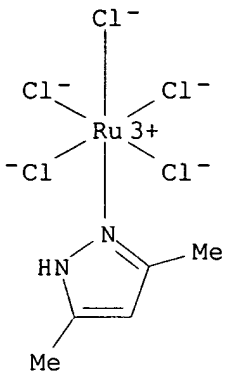
CRN 67-51-6
CMF C5 H8 N2



RN 124875-16-7 HCAPLUS
CN Ruthenate(2-), pentachloro(3,5-dimethyl-1H-pyrazole-N2)-, (OC-6-21)-, dihydrogen, compd. with 3,5-dimethyl-1H-pyrazole (1:1) (9CI) (CA INDEX NAME)

CM 1

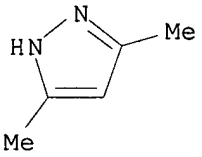
CRN 124875-15-6
CMF C5 H8 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

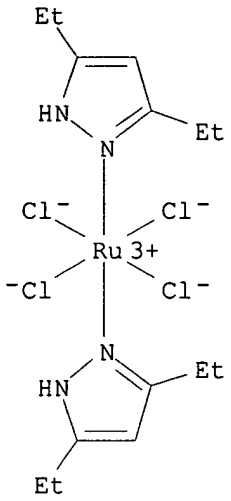
CRN 67-51-6
CMF C5 H8 N2

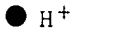


RN 124875-18-9 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(3,5-diethyl-1H-pyrazole-N2)-, (OC-6-11)-, hydrogen, compd. with 3,5-diethyl-1H-pyrazole (1:1) (9CI) (CA INDEX NAME)

CM 1

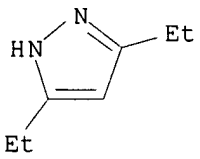
CRN 124875-17-8
CMF C14 H24 Cl4 N4 Ru . H
CCI CCS





CM 2

CRN 2817-73-4
CMF C7 H12 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

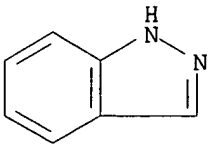
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

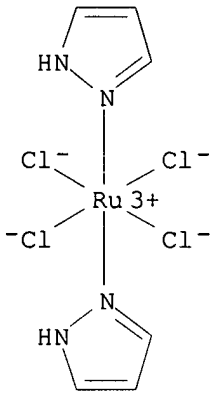
CRN 271-44-3
CMF C7 H6 N2



RN 124951-57-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-pyrazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-pyrazole (1:1) (9CI) (CA INDEX NAME)

CM 1

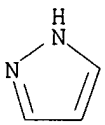
CRN 124951-56-0
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H+

CM 2

CRN 288-13-1
CMF C3 H4 N2

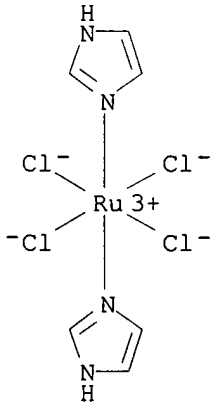


L77 ANSWER 48 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1989:586904 HCAPLUS
DN 111:186904
TI Efficacy of new ruthenium complexes against chemically induced autochthonous colorectal carcinoma in rats
AU Berger, Martin R.; Garzon, Felix T.; **Keppler, Bernhard K.**;

Schmaehl, Dietrich
CS Inst. Toxicol. Chemother., Ger. Cancer Res. Cent., Heidelberg, 6900, Fed. Rep. Ger.
SO Anticancer Research (**1989**), 9(3), 761-5
CODEN: ANTRD4; ISSN: 0250-7005
DT Journal
LA English
AB SD rats bearing acetoxymethylmethylnitrosamine-induced colorectal carcinomas were treated by i.v. administration of trans-imidazoliumbisimidazoletetrachlororuthenate(III) [ImH(RuIm2Cl4)], bisbenzimidazoliumbenzimidazolepentachlororuthenate(III) [(BzImH)2(RuBzImCl5)] and trans-indazoliumbisindazoletetrachlororuthenate(III) [IndH(ruInd2Cl4)]. The dose levels used were 0.022 mmol/kg administered twice weekly over ten weeks for all compds. and, addnl., 0.015 mmol/kg for ImH(RuIm2Cl4). All compds. caused a tumor growth inhibition exceeding 90%; differences were found with regard to toxicity: ImH(RuIm2Cl4) and (BzImH)2(RuBzImCl5) caused dose-related decreases in body weight and increases in mortality as shown by 21% and 29% body weight loss compared to controls as well as 10% and 45% mortality for the two dosages of the first compound, and 9% body weight loss compared to controls as well as 7% mortality for the latter compound In contrast, equimolar administration of IndH(RuInd2Cl4) was not related to any symptoms of toxicity as evidenced by 2% body weight gain compared to controls as well as 0% mortality. Since this latter drug obviously showed remarkable activity in a highly resistant type of tumor at negligible toxicity, it certainly deserves special attention.
IT **103875-27-0 124875-20-3**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(antitumor activity and toxicity of, structure in relation to)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

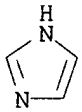
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



RN 124875-20-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-indazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-indazole (1:1) (9CI) (CA INDEX NAME)

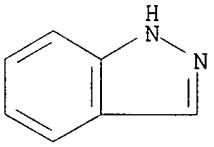
CM 1

CRN 124875-19-0
CMF C14 H12 Cl4 N4 Ru . H
CCI CCS

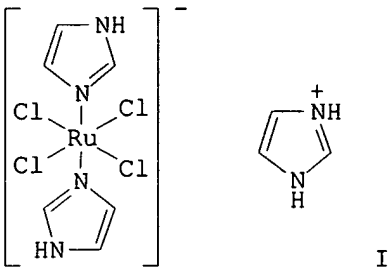
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 271-44-3
CMF C7 H6 N2



L77 ANSWER 49 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1988:68411 HCAPLUS
DN 108:68411
TI Comparative antitumor activity of ruthenium derivatives with 5'-deoxy-5-fluorouridine in chemically induced colorectal tumors in SD rats
AU Garzon, F. T.; Berger, M. R.; **Keppler, B. K.**; Schmaehl, D.
CS German Cancer Res. Cent., Inst. Toxicol. Chemotherapy, Heidelberg, D-6900, Fed. Rep. Ger.
SO Cancer Chemotherapy and Pharmacology (**1987**), 19(4), 347-9
CODEN: CCPHDZ; ISSN: 0344-5704
DT Journal
LA English
GI



I

AB The activity of a novel Ru compound (I) was compared with that of 5'-deoxy-5-fluorouridine (5'dFUR) in autochthonous acetoxymethyl(methylnitrosamine) (AMMN)-induced colorectal cancer in rats. I had considerable antitumor efficacy compared with 5'dFUR against the growth of AMMN-induced colorectal adenocarcinoma in SD rats. The mortality rates with I were dose-related, but its efficacy did not vary in all doses administered.

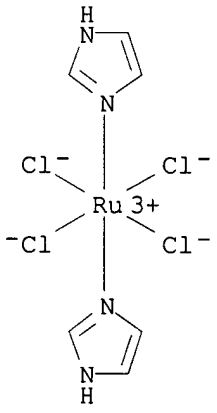
IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of, in colorectum)

RN 103875-27-0 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

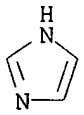
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

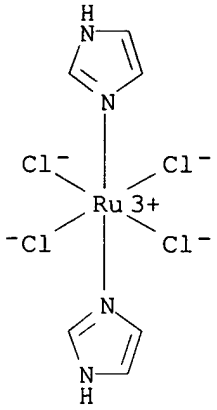
CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 50 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1987:648979 HCAPLUS
DN 107:248979
TI Synthesis, molecular structure, and tumor-inhibiting properties of imidazolium trans-bis(imidazole)tetrachlororuthenate(III) and its methyl-substituted derivatives
AU **Keppler, B. K.**; Rupp, W.; Juhl, U. M.; Endres, H.; Niebl, R.; Balzer, W.
CS Anorg.-Chem. Inst., Univ. Heidelberg, Heidelberg, 6900, Fed. Rep. Ger.
SO Inorganic Chemistry (**1987**), 26(26), 4366-70
CODEN: INOCAJ; ISSN: 0020-1669
DT Journal
LA English
AB The preparation, mol. structure, and antitumor activity of ImH[RuIm2Cl4] (I; Im = imidazole) and 4-MeImH[Ru(4-MeIm)2Cl4] (II; 4-MeIm = 4-methylimidazole) are described. I is monoclinic, C2/c, a 13.266(3), b 8.047(1), c 16.514(4) Å, β 112.53(2)°, Z = 4, d.(calculated) = 1.83 g cm-3, Rw = 0.029 for 1710 reflections and 106 parameters. II is monoclinic, P21/a, a 12.947(3), b 10.484(3), c 14.170(4) Å, β 108.22(2)°, Z = 4, d.(calculated) = 1.78 g cm-3, Rw = 0.039 for 2563 reflections and 211 parameters. The antitumor activity was studied in the P 388 leukemia model. The lifespan of the animals treated with ImH[RuIm2Cl4] was increased up to T/C values of 194%. The activity was in the same range as or was slightly better than in the case of cisplatin, which was tested as a pos. control. 5-Fluorouracil was less active compared to these metal complexes. 4-MeImH[Ru(4-MeIm)2Cl4] exhibited activity similar to that of ImH(RuIm2Cl4). The mechanism of action and the possible applications of these Ru complexes are discussed.
IT **103875-27-0P 111137-62-3P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and crystal structure and antitumor activity of)
RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

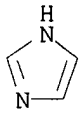
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

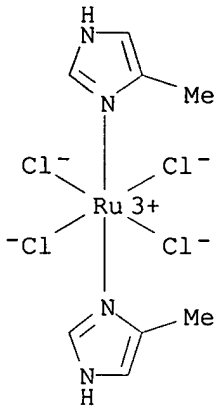
CRN 288-32-4
CMF C3 H4 N2



RN 111137-62-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(4-methyl-1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 4-methyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

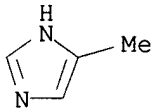
CRN 111137-61-2
CMF C8 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

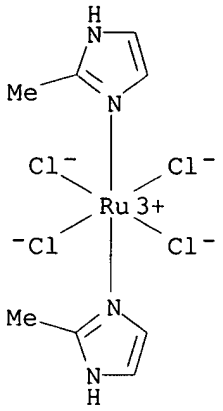
CRN 822-36-6
CMF C4 H6 N2



IT **111137-60-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 111137-60-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2-methyl-1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 2-methyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

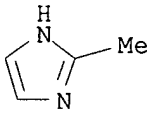
CM 1

CRN 111137-59-8
CMF C8 H12 Cl4 N4 Ru . H
CCI CCS



CM 2

CRN 693-98-1
CMF C4 H6 N2

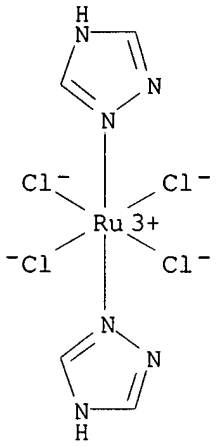


L77 ANSWER 51 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1987:568354 HCAPLUS
DN 107:168354
TI Synthesis and antitumor activity of triazolium-bis(triazole)tetrachlororuthenate(III) and bistriazolium-triazolepentachlororuthenate(III). Two representatives of a new class of inorganic antitumor agents
AU **Keppler, B. K.**; Balzer, W.; Seifried, V.
CS Anorg.-Chem. Inst., Univ. Heidelberg, Heidelberg, Fed. Rep. Ger.
SO Arzneimittel-Forschung (**1987**), 37(7), 770-1
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
AB The synthesis of the two water-soluble heterocycle coordinated ruthenium complexes triazolium-bis(triazole) tetrachlororuthenate(III), TrH(RuTr2Cl4), and bistriazolium-triazolepentachlororuthenate(III), (TrH)2(RuTrCl5), is described. For these 2 complexes, antitumor activity against the P388 leukemia model was observed with increase in lifespan of 137% to 150%, resp., compared with 144% and 175%, resp., for 5-FU and cisplatin.
IT **110649-85-9P 110670-30-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and neoplasm-inhibitory activity of)
RN 110649-85-9 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-1,2,4-triazole-κN2)-, (OC-6-11)-, hydrogen, compd. with 1H-1,2,4-triazole (1:1) (9CI) (CA INDEX NAME)

CM 1

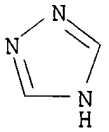
CRN 110649-84-8
CMF C4 H6 Cl4 N6 Ru . H
CCI CCS



● H^+

CM 2

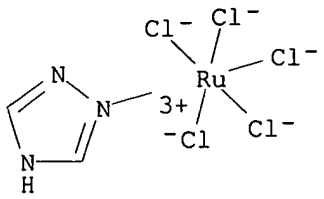
CRN 288-88-0
CMF C2 H3 N3



RN 110670-30-9 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-1,2,4-triazole-N2)-, (OC-6-21)-, dihydrogen, compd. with 1H-1,2,4-triazole (1:2) (9CI) (CA INDEX NAME)

CM 1

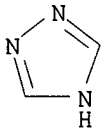
CRN 110670-29-6
CMF C2 H3 Cl5 N3 Ru . 2 H
CCI CCS



●2 H^+

CM 2

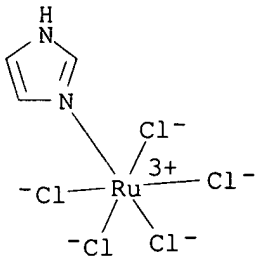
CRN 288-88-0
CMF C2 H3 N3



L77 ANSWER 52 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1987:112595 HCAPLUS
DN 106:112595
TI Synthesis, antitumor activity, and x-ray structure of bis(imidazolium) (imidazole)pentachlororuthenate(III), (ImH)2(RuImCl5)
AU **Keppler, B. K.**; Wehe, D.; Endres, H.; Rupp, W.
CS Anorg. Chem. Inst., Univ. Heidelberg, Heidelberg, 6900, Fed. Rep. Ger.
SO Inorganic Chemistry (**1987**), 26(6), 844-6
CODEN: INOCAJ; ISSN: 0020-1669
DT Journal
LA English
AB The x-ray structure, an improved preparation, and the antitumor activity of (ImH)2(RuImCl5) (I; Im = imidazole) are described. Crystals of I are orthorhombic, space group Bm21b, with a 8.464(2), b 14.406(3), c 14.936(4) Å, Z = 4, d.(calculated) = 1.77 g cm-3, and final Rw = 0.038, for 764 reflections and 75 variables. The antitumor activity was studied in the P 388 leukemia model. The lifespan of the animals treated with I was increased up to T/C values of 150-162%. This effect was in the same range as that observed with the pos. controls 5-fluorouracil and cisplatin. These clin. used drugs increased the lifespan in the same experiment up to T/C values of 144% and 175%, resp.
IT **105085-56-1P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(improved preparation, crystal structure and antitumor activity of)
RN 105085-56-1 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-imidazole-N3)-, (OC-6-21)-, dihydrogen, compd. with 1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

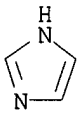
CRN 105085-55-0
CMF C3 H4 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 53 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1987:61212 HCAPLUS
DN 106:61212
TI Ruthenium compounds having a tumor inhibiting activity
IN Keller, Heimo J.; **Keppler, Bernhard**
PA Byk-Gulden Lomberg Chemische Fabrik G.m.b.H., Fed. Rep. Ger.
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 8600905	A1	19860213	WO 1985-EP369	19850724	<--
	W: AU, DK, FI, JP, NO, US					
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
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	AU 570826	B2	19880324			
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	EP 191096	B1	19890913			
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE					
	JP 61502761	T2	19861127	JP 1985-503999	19850724	<--
	JP 06094471	B4	19941124			

	AT 46343	E	19890915	AT 1985-904433	19850724 <--
	US 4843069	A	19890627	US 1986-849455	19860425 <--
PRAI	CH 1984-3594	A	19840724 <--		
	CH 1985-2907	A	19850704 <--		
	EP 1985-904433	A	19850724 <--		
	WO 1985-EP369	A	19850724 <--		

AB Complexes of Ru halides with N-containing heterocyclic compds. are prepared as tumor inhibitors. For example, 1,2,4-triazoliumtetrachlorobis(1,2,4-triazole)ruthenate (I) administered to mice at 45.1 mg/kg i.p. on days 1,5,9 after i.p. inoculation with 106 P388 leukemia cells, increased the life span of the mice by 61%. I was prepared by adding 1,2,4-triazole to a HCL solution of RuCl2.

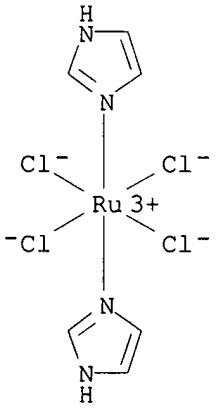
IT **103875-27-0P 105085-40-3P 105085-46-9P**
105085-48-1P 105085-50-5P 105085-52-7P
105085-54-9P 105085-56-1P
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as neoplasm inhibitor)

RN 103875-27-0 HCAPLUS

CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

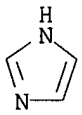
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

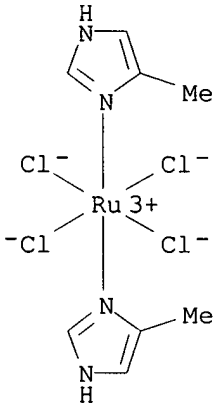
CRN 288-32-4
CMF C3 H4 N2



RN 105085-40-3 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(4-methyl-1H-imidazole-N3)-, hydrogen, compd. with 4-methyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

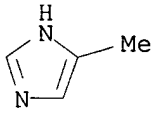
CRN 105085-39-0
CMF C8 H12 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 822-36-6
CMF C4 H6 N2

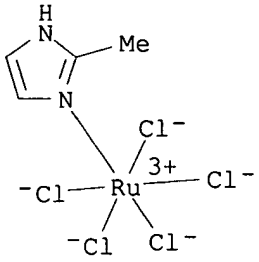


RN 105085-46-9 HCAPLUS
CN Ruthenate(2-), pentachloro(2-methyl-1H-imidazole-κN3)-, (OC-6-21)-, dihydrogen, compd. with 2-methyl-1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 105085-45-8
CMF C4 H6 Cl5 N2 Ru . 2 H

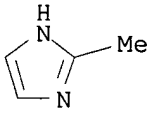
CCI CCS



●2 H^+

CM 2

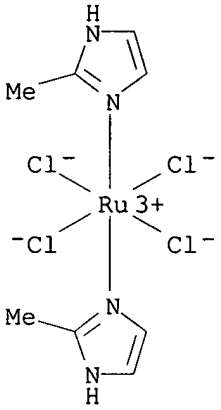
CRN 693-98-1
CMF C4 H6 N2



RN 105085-48-1 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(2-methyl-1H-imidazole-κN3)-, hydrogen, compd. with 2-methyl-1H-imidazole (1:1) (9CI) (CA INDEX NAME)

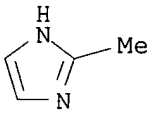
CM 1

CRN 105085-47-0
CMF C8 H12 Cl4 N4 Ru . H
CCI CCS



CM 2

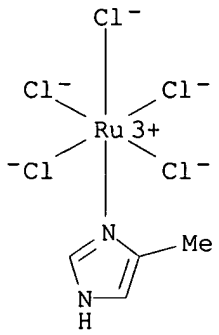
CRN 693-98-1
CMF C4 H6 N2



RN 105085-50-5 HCAPLUS
CN Ruthenate(2-), pentachloro(4-methyl-1H-imidazole-N3)-, (OC-6-21)-, dihydrogen, compd. with 4-methyl-1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

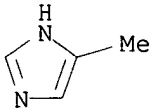
CRN 105085-49-2
CMF C4 H6 Cl5 N2 Ru . 2 H
CCI CCS



● 2 H^+

CM 2

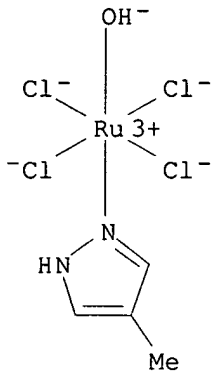
CRN 822-36-6
CMF C4 H6 N2



RN 105085-52-7 HCAPLUS
CN Ruthenate(2-), tetrachlorohydroxy(4-methyl-1H-pyrazole-N2)-, dihydrogen, compd. with 4-methyl-1H-pyrazole (1:2) (9CI) (CA INDEX NAME)

CM 1

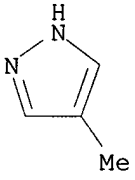
CRN 105085-51-6
CMF C4 H7 Cl4 N2 O Ru . 2 H
CCI CCS



●2 H^+

CM 2

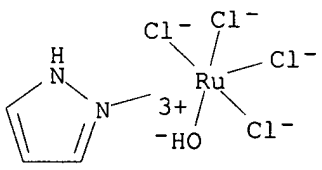
CRN 7554-65-6
CMF C4 H6 N2



RN 105085-54-9 HCAPLUS
CN Ruthenate(2-), tetrachlorohydroxy(1H-pyrazole-N2)-, dihydrogen, compd. with 1H-pyrazole (1:2) (9CI) (CA INDEX NAME)

CM 1

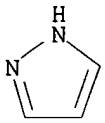
CRN 105085-53-8
CMF C3 H5 Cl4 N2 O Ru . 2 H
CCI CCS



●2 H^+

CM 2

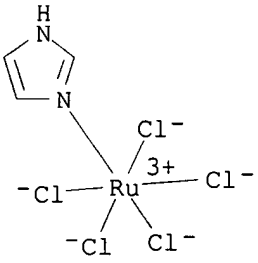
CRN 288-13-1
CMF C3 H4 N2



RN 105085-56-1 HCAPLUS
CN Ruthenate(2-), pentachloro(1H-imidazole-N3)-, (OC-6-21)-, dihydrogen, compd. with 1H-imidazole (1:2) (9CI) (CA INDEX NAME)

CM 1

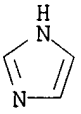
CRN 105085-55-0
CMF C3 H4 Cl5 N2 Ru . 2 H
CCI CCS



●2 H^+

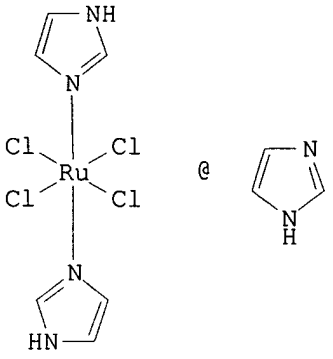
CM 2

CRN 288-32-4
CMF C3 H4 N2



L77 ANSWER 54 OF 54 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1986:490867 HCAPLUS
DN 105:90867
TI Antitumor activity of imidazolium-bisimidazole-tetrachlororuthenate(III). A representative of a new class of inorganic antitumor agents
AU **Keppler, B. K.**; Rupp, W.

CS Anorg.-Chem. Inst., Univ. Heidelberg, Heidelberg, D-6900, Fed. Rep. Ger.
SO Journal of Cancer Research and Clinical Oncology (**1986**), 111(2), 166-8
CODEN: JCROD7; ISSN: 0171-5216
DT Journal
LA English
GI



I

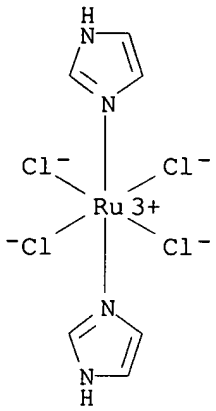
AB The antitumor activity of imidazoliumbisimidazoletetrachlororuthenate(III) (I) [**103875-27-0**] against the P388 leukemia and against the B16 melanoma was investigated. The test compound showed high activity against these tumor models. The tumor inhibiting effect was better than or equal to the effects of cyclophosphamide, cisplatin, or 5-fluorouracil. The effective substance is a new, water soluble, anionic, nitrogen-heterocyclic coordinated, Ru species, exhibiting antitumor activity.

IT **103875-27-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(as neoplasm inhibitor)

RN 103875-27-0 HCAPLUS
CN Ruthenate(1-), tetrachlorobis(1H-imidazole-κN3)-, (OC-6-11)-, hydrogen, compd. with 1H-imidazole (1:1) (9CI) (CA INDEX NAME)

CM 1

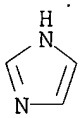
CRN 103875-26-9
CMF C6 H8 Cl4 N4 Ru . H
CCI CCS



● H^+

CM 2

CRN 288-32-4
CMF C3 H4 N2



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=> d his

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               E KEPPLER B/AU
L2           219 S E3-E10
               E KEPLER B/AU
               E FAUSTUS/PA,CS
L3            14 S E3-E16
               SEL RN L1

     FILE 'REGISTRY' ENTERED AT 14:52:52 ON 07 DEC 2005
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L5             1 S L4 AND CCS/CI
L6             1 S 189556-38-5
L7             9 S 189556-38-5/CRN
L8             1 S L4 NOT RU/ELS
L9             1 S PYRAZOLE/CN
               E INDAZOLE/CN
L10            1 S E3
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                E IMIDAZOLE/CN
L11           1 S E3
                E TRAZOLE/CN
                E TRIAZOLE/CN
L12           1 S E3
L13        1407 S (N3C2 OR N2CNC)/ES AND 1/NR AND 3/ELC.SUB
L14          71 S L13 AND 3/N AND 2/C
L15          51 S L14 AND 1/NC
L16          44 S L15 AND (C AND N AND H)/ELS
L17          41 S L16 NOT (PMS OR IDS)/CI
L18          31 S L17 NOT ((D OR T)/ELS OR 11C# OR 13C# OR 14C# OR C11# OR C13#
L19          26 S L18 NOT RPS/CI
L20          22 S L19 NOT ION
L21          21 S L20 NOT 15N2
L22          16 S L21 NOT IUM
                SEL RID
L23          61 S E1-E11 AND RU/ELS
L24        3025 S (333.161 OR 16.165 OR 16.195)/RID AND RU/ELS
L25         816 S (333.161.31 OR 16.165.12 OR 16.195.24)/RID AND RU/ELS
L26         877 S L23,L25
L27             STR
L28          12 S L27 SAM SUB=L26
L29         245 S L27 FUL SUB=L26
                SAV TEMP L29 SHIAO627/A
L30           2 S L4 AND RU/ELS NOT RU/MF
L31         245 S L5-L7,L30,L29

     FILE 'HCAPLUS' ENTERED AT 15:08:16 ON 07 DEC 2005
L32         191 S L31
L33          54 S L32 AND L1-L3
L34          13 S KP1019 OR KP 1019

     FILE 'REGISTRY' ENTERED AT 15:09:26 ON 07 DEC 2005
L35           1 S 124875-20-3

     FILE 'HCAPLUS' ENTERED AT 15:09:35 ON 07 DEC 2005
L36          34 S L35
L37          36 S L34,L36
L38          25 S L37 AND (PY<=2001 OR PRY<=2001 OR AY<=2001)
L39         133 S L32 AND (PY<=2001 OR PRY<=2001 OR AY<=2001)
L40         131 S L32 AND (PD<=20010126 OR PRD<=20010126 OR AD<=20010126)
L41          25 S L37 AND (PD<=20010126 OR PRD<=20010126 OR AD<=20010126)
L42          68 S L31(L)PREP+NT/RL
L43          86 S L31(L)(THU OR BAC OR DMA OR PAC OR PKT)/RL
L44         117 S L32 AND (PHARMACEUT? OR PHARMACOL? OR PATHOL?)/SC,SX,CW,CT
                E NEOPLASM INHIBITOR/CT
L45       77032 S E4-E6
                E E4+ALL
                E E2+ALL
L46      182155 S E3 OR E41+OLD,NT OR E42+OLD,NT OR E43+OLD,NT OR E45+OLD,NT
L47          65 S L39 AND L45,L46
L48          28 S L37 AND L45,L46
L49          18 S L41 AND L48
L50          74 S L42-L44 AND L47-L49
L51          33 S L1-L3 AND L37
L52          40 S L33,L51 AND L40,L41
L53          84 S L50,L52
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:17:34 ON 07 DEC 2005
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L54          59 S E1-E59
L55          11 S L54 AND S/ELS
L56          48 S L54 NOT L55
L57           6 S L56 AND (C28H24CL2N8RU OR C3H4CL4N3ORU)
L58          42 S L56 NOT L57
L59           3 S L58 AND (C21H18CL3N6RU OR C16H15CL3N5RU)
L60          39 S L58 NOT L59

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L61          78 S L60
L62          61 S L61 AND (PD<=20010126 OR PRD<=20010126 OR AD<=20010126)
L63          45 S L62 AND L45,L46
L64          32 S L60 (L) (THU OR BAC OR DMA OR PAC OR PKT)/RL AND L62
L65          53 S L62 AND (PHARMACEUT? OR PHARMACOL? OR PATHOL?)/SC,SX,CW,CT
L66          40 S L1-L3 AND L62
L67          61 S L41,L62-L66
L68          54 S L67 NOT P/DT
L69           7 S L67 NOT L68
L70           5 S L69 NOT (IMMUNOSUPP? OR HYPERPROLIFERAT?)
L71          36 S L68 AND L1-L3
L72           2 S L71 NOT ?TUMOR?
L73          34 S L71 NOT L72
L74          18 S L68 NOT L69-L73
L75           3 S L74 NOT ?TUMOR?
L76          15 S L74 NOT L75
L77          54 S L70,L73,L76

     FILE 'MEDLINE' ENTERED AT 15:36:54 ON 07 DEC 2005
L78           8 S L34 OR L35
L79           2 S L78 AND PY<=2001
L80           2 S L79 AND KEPPLER ?/AU

     FILE 'CANCERLIT' ENTERED AT 15:38:08 ON 07 DEC 2005
L81           3 S L78
L82           1 S L81 NOT MEDLINE/OS
L83           1 S L82 AND KEPPLER ?/AU

     FILE 'EMBASE' ENTERED AT 15:38:39 ON 07 DEC 2005
L84          12 S L78
L85          16 S "INDAZOLIUM TETRACHLOROBIS(INDAZOLE)RUTHENATE"/CT
L86          11 S L84,L85 AND PY<=2001
L87           4 S L86 AND KEPPLER ?/AU
L88          11 S L86,L87
L89          11 S L88 AND (?NEOPLAS? OR ?TUMOR? OR ?CANCER?)

     FILE 'REGISTRY' ENTERED AT 15:40:44 ON 07 DEC 2005

     FILE 'MEDLINE, CANCERLIT, EMBASE' ENTERED AT 15:41:27 ON 07 DEC 2005
L90          12 DUP REM L80 L83 L89 (2 DUPLICATES REMOVED)

     FILE 'HCAPLUS' ENTERED AT 15:41:37 ON 07 DEC 2005

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